Catalytic Asymmetric Synthesis of α-Amino Acids

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Received November 29, 2006

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1. Introduction

Proteinogenic and non-proteinogenic α-amino acids (α-AAs) constitute one of the five most important families of natural products[1] and are essential molecules in many scientific areas. They are continuously employed in the elaboration of peptides and proteins as chiral catalysts and as chiral pool in the ligand design and total synthesis.[2] The impressive number of applications of the enantiomerically enriched α-AAs have attracted a great deal of attention among scientists. Particularly, the increasing demand of these optically active compounds prompted the synthetic organic chemists to develop new methodologies.[3] Basically, α-AAs can be obtained through the so-called classical methods, that means, chemical and enzymatic resolutions, isolation of α-AAs from natural sources, and employing asymmetric synthesis. The historical overview about the elaboration of enantiopure α-AAs can be classified into three periods. First, the classical methods were enormously employed before 1980 and at the beginning of the 1980s. Second, the diastereoselective synthesis of α-AAs, based on the design of chiral templates derived from glycine, alanine, and other α-AAs, raised the maximum interest during the last two decades. However, catalytic enantioselective methods, especially the catalytic hydrogenations (known since 1968), organocatalysis, and phase transfer catalysis (PTC) of racemic α-imino esters, have been overwhelmingly preferred in a third period, covering the last 15 years (Figure 1).

In light of these antecedents, the catalytic asymmetric synthesis constitutes the most versatile and powerful way to achieve all sorts of optically enriched α-AAs *versus* biotechnological processes and chemical resolution of racemic mixtures. The explosive growth undergone by this exciting area is mainly due to the enormous effort dedicated to asymmetric catalysis.[4] Most of the enantioselective catalysts are metal complexes containing chiral organic ligands or chiral organic molecules (recently named organocatalysts).

10.1021/cr050580o CCC: $65.00
Published on Web 10/04/2007

Carmen Nájera (left) obtained her B.Sc. at the University of Zaragoza in 1973 and her Ph.D. at the University of Oviedo with J. Barluenga and M. Yus in 1979. She performed postdoctoral work at the ETH (Zurich) with D. Seebach, at the Dyson Perrins Laboratory (Oxford) with J. E. Baldwin, at Harvard University with E. J. Corey, and at Uppsala University with J.-E. Bäckvall. She was promoted to Associate Professor in 1985 at the University of Oviedo and Full Professor in 1993 at the University of Alicante. She has held visiting Professorships at the University of Arizona in Tucson (USA), Universidad Nacional del Sur in Bahía Blanca (Argentina), Louis Pasteur University in Strasbourg (France), and Ecole Nationale Superiéure de Chimie de Paris (France). She is coauthor of *ca.* 200 papers and 30 reviews and has supervised the work of 23 Ph.D. students. She was awarded with the "2006 Janssen Cilag Organic Chemistry Prize" from the Spanish Royal Chemical Society of Chemistry and the "2006 Rosalind Franklin International Lectureship" from the English Royal Society. She is cofounder of a new chemical company MEDALCHEMY, S. L., as a spin-off of the University of Alicante. Her current research interest focuses on sulfones, amino acids, asymmetric catalysis, and palladium catalysis.

José Miguel Sansano (right) was born in Rojales (Alicante), Spain, in 1965. He studied chemistry at the University of Alicante, where he obtained his B.Sc. and Ph.D. degrees in 1988 and 1994, respectively. After spending a 2-year postdoctoral stay at the University of Leeds (U.K.) with Prof. R. Grigg, he joined the University of Alicante in 1996, where he was appointed Associate Professor in 2001. He is cofounder of a new chemical company MEDALCHEMY, S. L., as a spin-off of the University of Alicante. His current research interests include asymmetric synthesis, sulfones, amino acids, and organometallic chemistry.

An ideal chiral ligand or chiral organocatalyst should not only be accessible, but it should also be possible to modify its structure systematically. In this way, the catalyst structure can be adapted to a specific application or a substrate structure. Thus, this fine-tuning modulation, together with the minimal amount required of it in each reaction, the catalytic efficiency (turnover number or turnover frequency), the reproducibility of the catalytic transformation, the accessibility of the catalyst, the application range, the functional group tolerance, and the recovering of the unaltered catalyst (or chiral ligand) are the most important features for ensuring a successful highly enantioselective process in both laboratory and industrial scales.

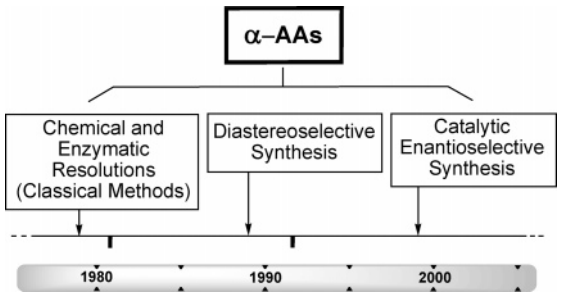


Figure 1. Historical overview of the generation of enantiomerically enriched α-AA.

The association of the two concepts amino acid synthesis and enantioselective catalysis, the subject of this review, tries to imitate the biosynthetic natural process, and many fascinating aspects are being continuously discovered. However, the rational design of a catalyst for a specific reaction is very tedious and difficult; for that reason, combinatorial chemistry, which would allow the screening of large catalyst libraries for enantioselectivity and reactivity, is currently being developed with some promising results.[5]

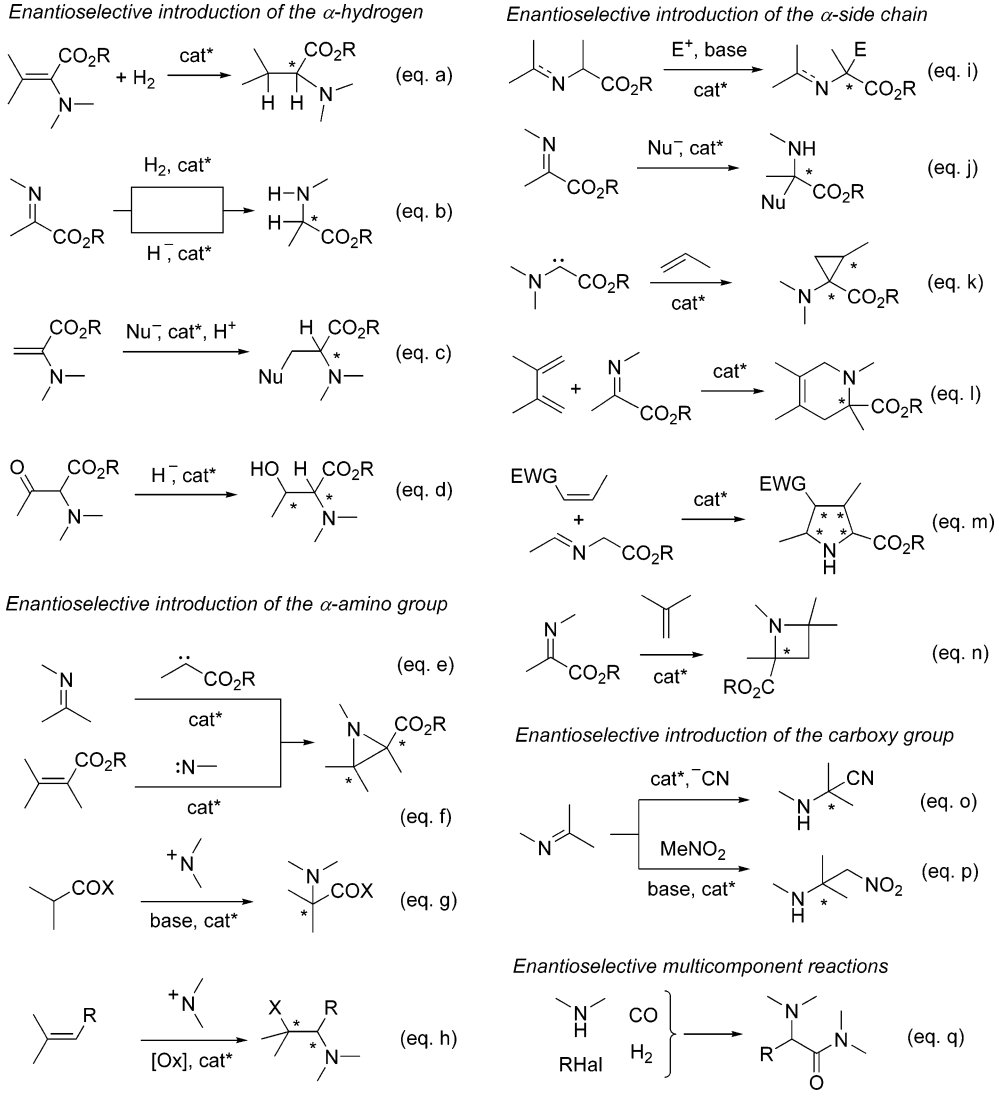
Although enzymes are a valuable class of enantioselective catalysts, the coverage of biocatalysts,[6] which are considered as an alternative to synthetic chiral catalysts, is beyond the scope of this review. In this work, we will compile the contributions appearing in the literature up to 2005, where an α-AA or a direct derivative of it could be obtained through catalytic enantioselective routes. The contents of the main body of the text, summarized in Scheme 1, include different approaches based on the fragment of the α-AA introduced through the enantioselective process and a more comprehensive coverage than the well focused minireview published by Ma 3 years ago.[3g]

The first strategy consists in the enantioselective introduction of the α-hydrogen, which involved the enantioselective hydrogenation of carbon−carbon double bonds (Scheme 1, eq a), the analogous hydrogenation or hydride addition onto carbon−nitrogen double bonds (Scheme 1, eq b), and the protonation of chiral enolates, generated in substoichiometric amounts through catalyzed Michael additions followed by enantioselective protonation or by a combined carbonyl hydrogenation−dynamic kinetic resolution (DKR) of racemic α-amino-1,3-dicarbonyl compounds (Scheme 1, eqs c and d, respectively). The second group of transformations involves whatever methodology is able to introduce enantioselectively the nitrogen atom, such as, for example the two methods to generate aziridines employing carbenes or nitrenes onto imines or electrophilic alkenes (Scheme 1, eqs e and f, respectively). The introduction of the nitrogen atom can be achieved by reaction of enolates onto electrophilic nitrogen-containing species, such as it is exemplified in Scheme 1, eq g. Enantioselective aminohydroxylation and diamination are two different sequences with different historical background; while the aminohydroxylation reaction is very well-known and conveniently controlled, the enantioselective diamination is yet in its infancy (Scheme 1, eq h).

2. Enantioselective Introduction of the α-Hydrogen

The most abundant transformations leading to α-AAs by the enantioselective introduction of the α-hydrogen are overwhelmingly the carbon−carbon double bond hydrogenations of the corresponding α,β-dehydro-α-amino acid (DAA) derivatives [also known as α,β-didehydro-α-amino acid (DDAA) derivatives], although some examples of the direct carbon−nitrogen double bond hydrogenations are also known (Scheme 1, eqs a and b). The reductive amination of α-keto acids or α-keto esters (Scheme 1, eq b) is considered as a good strategy, but it has not been as exploited as the previous transformation. The enantioselective protonation of the resulting alkene, generated after the nucleophilic attack onto

Scheme 1. Different Synthetic Catalytic Enantioselective Approaches for the Preparation of Enantiomerically Enriched α-AAs

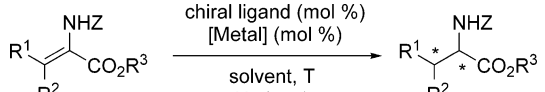


DAA derivatives (Scheme 1, eq c) or generated as an intermediate in the enantioselective catalyzed reduction−DKR of α-amino-1,3-dicarbonyl compounds (Scheme 1, eq d), is also known, although it has been studied in lesser extension.

2.1. Metal-Catalyzed Asymmetric Hydrogenation of DAA Derivatives

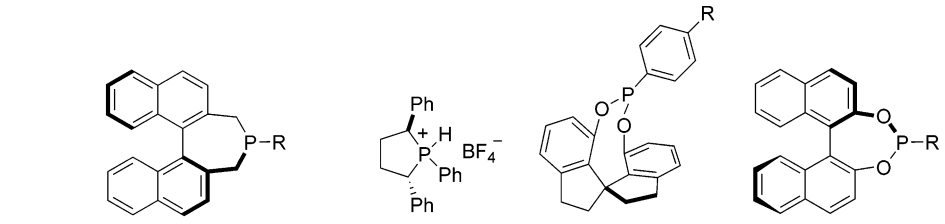
There is no doubt that hydrogen is the cleanest reducing agent and hydrogenation is one of the most important catalytic enantioselective methods in synthetic organic chemistry in the laboratory and in the production scale. Other typical features, such as the small amount of the catalyst and solvent, make this reaction more attractive. Nowadays, a considerable number of industrial processes are using asymmetric hydrogenations as a key step. Since the pioneering work of Knowles,[7] about the industrial manufacture of L-Dopa employing the Dipamp−[Rh] complex as catalyst, Horner[8] (using *P*-stereogenic ligands), and Kagan[9] (employing C_2 chiral phosphanes), many efforts to develop suitable chiral ligands for this general enantioselective hydrogenation of DAA derivatives have been made. These contributions culminated in the 2001 Nobel Prize to Knowles and Noyori and shared by Sharpless for his known enantioselective catalytic oxidation (see below). At the moment, this reaction represents one of the two more important and studied ways

Scheme 2



a; $R^1 = R^2 = H$, $R^3 = Me$, Z = Ac
b; $R^1 = R^2 = R^3 = H$, Z = Ac
c; $R^1 = Ph$, $R^2 = H$, $R^3 = Me$, Z = Ac
d; $R^1 = Ph$, $R^2 = R^3 = H$, Z = Ac
e; $R^1 = R^2 = R^3 = Me$, Z = Ac
f; $R^1 = Ar$, $R^2 = H$, $R^3 = Me$, Z = PhCO
g; $R^1 = R^2 = R^3 = Me$, Z = Cbz
h; R^1–R^2 = -$(CH_2)_4$-, $R^3 = Me$, Z = Ac
i; R^1–R^2 = -$(CH_2)_5$-, $R^3 = Me$, Z = Ac

to achieve enantiomerically enriched α-AAs. A considerable number of reviews concerning enantioselective hydrogenations appear every year[10] with the aim of covering this prolific and extensive area of the asymmetric synthesis but focused on perspectives unique to the synthesis of α-AAs. The contributions appearing during the last 3 years involving this enantioselective carbon−carbon double bond hydrogenation of DAA derivatives **1** (Scheme 2) will be detailed according to the metal center and the nature of the chiral ligand−transition metal interaction during the elaboration of the catalytic complex.



(*S*$_a$)-**3**
a; R = Et. **b**; R = ^{i}Pr
c; R = ^{t}Bu. **d**; R = Ph
e; R = 4-MeO-C_6H_4
f; R = 4-(CF_3)-C_6H_4
g; R = 3,5-Me_2-C_6H_3
h; R = 3,5-$^t Bu_2$-C_6H_3
i; R = 2-MeO-C_6H_4
j; R = 2-F-C_6H_4
k; R = 4-F-C_6H_4
l; R = 2-Naphthyl
m; R = 3-MeO-C_6H_4
n; R = 3,4-$(MeO)_2C_6H_3$

(*S*$_a$)-**4**
a; R = NMe_2
b; R = NEt_2
c; R = N^iPr_2
d; R =
e; R =
f; R =

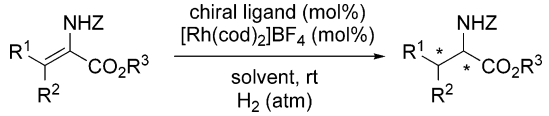
(*S*,*S*)-**5**

(*S*$_a$)-**6**
a; R = H
b; R = Me
c; R = OMe
d; R = Cl
e; R = CF_3

(*R*$_a$)-**7**
a; R = Me
b; R = ^{i}Pr
c; R = ^{t}Bu
d; R = Cy
e; R = Ph

Figure 2. Monodentate ligands containing at least a P−C bond.

Table 1. Enantioselective Synthesis of Compounds 2 Using Ligands 3−7 Complexed with [Rh]



1 **2**

			1 (Z = Ac)					product **2**			
entry	ligand (mol %)	[Rh][a] (mol %)	R^1	R^2	R^3	solvent[b]	P_{H_2} (atm)	conv (%)	config	ee (%)	ref
1	(*S*$_a$)-**3** (2)	1	H	H	Me	MePh	1	>99	(*R*)	up to 94	11
2	(*S*$_a$)-**3** (2)	1	Ph	H	Me	MePh	1	>99	(*R*)	up to 95	11
3	(*S*$_a$)-**4** (1−2)	0.5−1	Ph	H	Me	MePh/SDS[c]	1	100	(*R*)	up to 96	12
4	(*S*$_a$)-**4** (2)	1	H	H	Me	THF	1	100	(*R*)	up to 71	12
5	(*S*,*S*)-**5** (2.2)	1	Ph	H	Me	MeOH	1	100	(*R*)	up to 90	13
6	(*S*$_a$)-**6** (2)	1	Ph	H	Me	MePh	10	98	(*S*)	up to 99	14
7	(*S*$_a$)-**6** (2)	1	Ar	H	Me	MePh	10	98	(*S*)	97−99	14
8	(*R*$_a$)-**7** (4)	2	Me	Me	Me	MePh/DCM[d]	60	99	(*S*)	up to 94	15
9	(*R*$_a$)-**7** (4)	2	-$(CH_2)_4$-		Me	MePh/DCM[d]	60	99	(*S*)	up to 97	15
10	(*R*$_a$)-**7** (4)	2	-$(CH_2)_5$-		Me	MePh/DCM[d]	60	99	(*S*)	up to 95	15

[a] [Rh] = $[Rh(cod)_2]BF_4$. [b] Reactions run at 25 °C. [c] SDS = sodium dodecyl sulfate. [d] Reaction run at 30 °C.

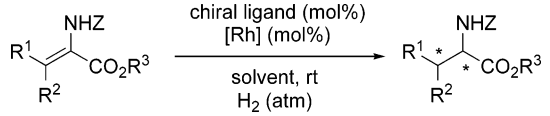
Recent experimental and computational data on the mechanism of Rh-catalyzed asymmetric hydrogenation of activated double bonds have been brought together in order to rationalize the present discrepancies in the prediction of the sense of enantioselection for the P-stereogenic ligands and the ligands with backbone chirality. At this moment, there are two possible alternative mechanisms: the "dihydride mechanism" and the "unsaturated mechanism". In the dihydride mechanism, the substrate is coordinated to a solvate−dihydride Rh complex, while, in the unsaturated mechanism, the hydrogen molecule is dissociated by the catalyst−substrate Rh complex. In both mechanisms, it is assumed that a fast equilibrium of the dihydride intermediates is followed by the stereodetermining migratory insertion step. This in turn makes possible a unified approach to predict the sense of the enantioselection *via* the Knowles quadrant diagrams.[10c]

It is well-known that the same ligand can evoke different results in a certain reaction, due to different reaction conditions (temperature, solvent, additives, etc.), but a modification of the chiral ligand can originate dramatic changes in the reaction product. In order to better understand the trends caused by these modifications, it is helpful to emphasize the following important ligand characteristics: (a) the dihedral angle (for chiral biaryl bidentate ligands) has a tremendous impact on both the enantioselection and the catalytic activity of the metal catalyst, establishing some correlations between this magnitude and the results obtained before; (b) the electronic properties of the ligand directly affect the reactivity of the complex; (c) the ligand pendants can modulate the steric hindrance during the approach of different reagents.[10b]

2.1.1. Chiral Monodentate Ligand–Rh Complexes

The enantioselective carbon−carbon bond hydrogenations of DAAs **1** by means of Rh complexes is a well understood process and constitutes a benchmark for the determination of the synthetic efficiency of such catalysts.[10h] Traditional monodentate chiral phosphines have been studied as ligands in these enantioselective processes,[10] but new phosphines **3**, aminophosphinites **4**, phosphonium salts **5**, and phosphonites **6** and **7** (Figure 2) formed Rh complexes with $[Rh(cod)_2]$-BF_4, which were successfully applied to the synthesis of α-AAs at room temperature with different enantioselection.[11−15] The more efficient catalyst of the series of compounds **3** was **3h** (R = 3,5-$^t BuC_6H_3$) (Table 1, entries 1 and 2),[11] whereas, for the aminophosphinites **4**, the dimethylamino derivative **4a** gave the best enantioselectivity (Table 1, entries

Table 2. Enantioselective Synthesis of Compounds 2 Using Phosphoramidite Ligands 8−19 Complexed with [Rh]



1 2

			1 (Z = Ac)					product **2**			
entry	ligand (mol %)	[Rh][a] (mol %)	R^1	R^2	R^3	solvent[b]	P_{H_2} (atm)	conv (%)	config	ee (%)	ref
1	(S_a)-**8a** (2)	1	Ar	H	Me	THF	20	99	(*R*)	92−99	17
2	(S_a)-**8b** (2)	1	Ar	H	Me[c]	THF	20	>99	(*R*)	97−100	17, 21
3	(S_a)-**8a** (1.2)	1	Ar	H	Me	DCM	5	99	(*R*)	92−99	18, 24
4	(S_a)-**8ag** (4)	2	H	H	Me	DCM	5	>99	(*R*)	99	19
5	(S_a)-**8ag** (4)	2	Ph	H	Me	DCM	5	>99	(*R*)	99	19
6	(S_a)-**8ah** (4)	2	H	H	Me	DCM	5	>99	(*R*)	99	19
7	(S_a)-**8ah** (4)	2	Ph	H	Me	DCM	5	>99	(*R*)	98	19
8	(R_a)-**8n** (4)	2	Me	Me	Me	MePh/DCM[d]	60	85	(*S*)	46	15
9	(S_a)-**8n** (1)	0.5	Ph	H	Me	DCM	2	98	(*R*)	89	20
10	(S_a)-**8a** (1)	0.5	Ph	H	Me	DCM	2	99	(*R*)	95	20
11	(R_a)-**9a**−**d** (0.2)	0.1	H	H	Me	DCM	1.3	100	(*S*)	97−99	22
12	(R_a)-**9a**−**d** (0.2)	0.1	Ar	H	Me	DCM	1.3	100	(*S*)	94−97	22
13	(*R*,*R*)-**10d** (2)	1	H	H	Me	DCM	20	>98	(*S*)	99	23
14	(*R*,*R*)-**10d** (2)	1	Me	H	Me	DCM	20	>98	(*S*)	98	23
15	(*R*,*R*)-**10d** (2)	1	Ar	H	Me	DCM	20	>98	(*S*)	96 to >99	23
16	(*R*,*R*)-**10f** (2)	1	Ar	H	Me	DCM	20	>98	(*S*)	96 to >99	23
17	(S_a,S_a)-**11** (1)	1	Ph	H	Me	DCM	20	100	(*R*)	97	24
18	(S_a,S_a)-**11** (1)	1	H	H	Me	DCM	20	100	(*R*)	95	24
19	(S_a,S_a)-**11** (1)	1	Me	H	Me	DCM	20	100	(*R*)	96	24
20	(S_a,S_a)-**11** (1)	1	Ar	H	Me	DCM	20	100	(*R*)	99	24
21	(*S*,*S*)-**12g** (2)	1	Ar	H	Me	DCM	5	100	(*R*)	89−92	25
22	(*S*,*S*)-**12g** (2)	1	H	H	Me	DCM	5	100	(*R*)	66	25
23	(S_a)-**13a** (2)	1	Ph	H	Me	DCM	5	100	(*R*)	98	26
24	(S_a)-**13a** (2)	1	3-F-C_6H_4	H	H	DCM	5	100	(*R*)	96	26
25	(R_a)-**15** (2)	1[e]	H	H	Me	DCM	1.7	100	(*S*)	98	27
26	(R_a)-**15** (2)	1[e]	Ar	H	Me	DCM	1.7	100	(*S*)	98 to >99	27
27	(S_a)-**16a** (1)	0.5	Ar	H	Me	DCM[f]	1	100	(*S*)	98	28, 29
28	(S_a)-**16e-g** (1)	0.5	Ar	H	Me	DCM[f]	1	100	(*S*)	94−99	29
29	(S_a)-**8at**, (S_a)-**8au** (5)	5	H	H	Me	DCM	1	96−100	(*R*)	65−75	30
30	(S_a)-**8au** (5)	5	H	H	H	DCM	1	100	(*R*)	72	30
31	(S_a)-**8at**, (S_a)-**8au** (5)	5	Ph	H	Me	DCM	1	100	(*R*)	64−80	30
32	(S_a)-**8at**, (S_a)-**8au** (5)	5	Ph	H	H	MePh	1	100	(*R*)	50−74	30
33	(S_a)-**8av**, (S_a)-**8ax** (2)	1	H	H	H	MePh	40	100	(*R*)	96−97	31
34	(S_a)-**8av**, (S_a)-**8ax** (2)	1	Me	H	Me	MePh	40	100	(*R*)	94−95	31
35	(S_a)-**8av**, (S_a)-**8ax** (2)	1	Ph	H	Me	MePh	40	100	(*R*)	95−96	31
36	(R_a)-**17** (2.2)	1	Ph	H	Me	DCM	5	100	(*S*)	93	32
37	(R_a)-**18** (2.2)	1	Ph	H	Me	DCM	5	100	(*S*)	95	32
38	(S_a,*S*)-**19a**−**c** (1)	0.5	H	H	Me	DCM	1.3	100	(*R*)	98−99	34
39	(S_a,*S*)-**19d**−**f** (1)	0.5	H	H	Me	DCM	1.3	100	(*R*)	94 to >99	34

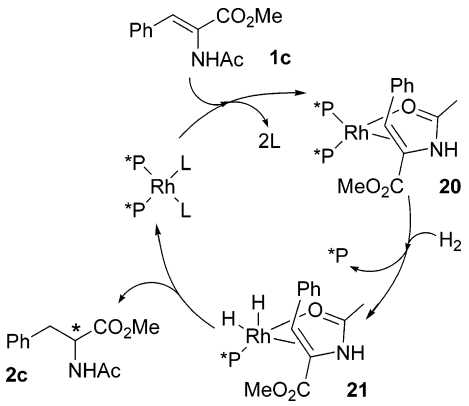
[a] [Rh] = [Rh(cod)$_2$]BF_4. [b] Reactions run at 25 °C. [c] Benzamide **1f** was used instead. [d] Reaction run at 30 °C. [e] [Rh] = [Rh(nbd)$_2$]BF_4 (nbd = norbornadienyl). [f] Reaction run at 0 °C.

3 and 4)[12] as well as the ligand **6c** (Table 1, entries 6 and 7)[14] and the simplest phosphonite **7a** (Table 1, entries 8−10).[15] However, from an operational point of view, the reactions performed with ligands **3**, **4**, and **5** are more convenient because they need 1 atm of hydrogen pressure, instead of the 100 and 60 atm required for the transformations mediated by ligands **6** and **7**, respectively. Achiral bisphosphine−Rh complexes with *N*-acetylphenylalaninate or camphorsulfonate as chiral counterions have been designed and used as catalysts in chiral matrices for the hydrogenation of DAA derivatives **1** with negligible enantioselection.[16]

Chiral Binol-derived phosphoramidites **8**−**19** (Figure 3) have been evaluated as ligands of Rh salts, mainly [Rh(cod)$_2$]-BF_4, as monodentate ligands in the Rh-catalyzed enantioselective hydrogenations of DAA derivatives **1** at room temperature. In spite of the fact that Monophos (*S*)-**8a** is considered as an excellent chiral ligand, phosphoramidite **8b** induced higher enantioselection (up to 99.9% ee) employing a hydrogen pressure of 20 atm in the mentioned asymmetric reaction (Table 2, entries 1 and 2), even using the acrylic benzamide **1f**, instead of the acetamide **1a**[17] (see Scheme 2). Monophos **8a** has also been employed, after a sequential Mizoroki−Heck reaction, in the synthesis of the very interesting enantiopure substituted phenylalanines (Table 2, entry 3).[18] From a library of monodentate chiral phosphoramidites **8a**−**c**, **8ad**−**8af**, **8ag**−**8am**, **8an**, **8ap**, and **8ar**, it was inferred that ligands (*S*)-**8ag** (Pipphos) and ligand (*S*)-**8ah** (Morfphos) afforded excellent and unprecedented enantioselectivities, under a moderate hydrogen pressure (5 atm), in the hydrogenation of *N*-acyl-DAA derivatives **1a** and **1c** (Table 2, entries 4−7).[19] However, for tetrasubstituted alkene **1g**, phosphoramidites **8** were not such effective ligands, affording a 46% ee as maximum enantioselection when **8n** was employed (Table 2, entry 8).[15]

Rh complexes of ligands (S_a)- and (R_a)-**8a** and **8n** were compared versus chiral bidentate ligand complexes such as Me-Duphos, JosiPhos, and PhanePhos (see below, Figures 11, 13, and 14) in kinetic studies of the catalytic enantiose-

Scheme 3



lective hydrogenation of compound **1c**, demonstrating that a bidentate phosphoramidite ligand is no longer a *conditio sine qua non* for achieving a fast and enantioselective hydrogenation of DAA derivatives (Table 2, entries 9 and 10).[20] Compounds **8b**, **8c**, **8e**, **8f**, and **8s** were the more appropriate ligands for hydrogenating acetamides **1** by using a new protocol for the synthesis of phosphoramidite libraries, which could prepare 96 phosphoramidites per day (Table 2, entry 2).[17,21]

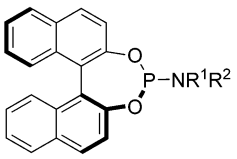
Binol-derived *N*-phosphinosulfoximines **9** have been prepared originally and tested in the asymmetric Rh-catalyzed hydrogenation of functionalized olefins **1**. Matched (R_a)-Binol/(*S*)-sulfur and mismatched (S_a)-Binol/(*S*)-sulfur combinations in molecules **9** concluded that the configuration at the sulfur atom played a small role in the catalytic enantioselective hydrogenation of acetamidoacrylate **1a** using a hydrogen pressure of 1.3 atm (Table 2, entries 11 and 12).[22] Another phosphoramidite family such as Depenphos (*R*,*R*)-**10a**−**h** were tested in the same Rh-catalyzed enantioselective hydrogenation of precursors **1**, with ligand **10d** being the most appropriate, furnishing, under high hydrogen pressure (20 atm), excellent ee's of the generated α-acetamido esters **2** in very high chemical yields (Table 2, entries 13−16).[23] Chiral bisphosphoramidite (S_a,S_a)-**11** can be considered as a monodentate ligand due to its linear structure and the optimal 1/2 [Rh]/ligand ratio needed for obtaining good results employing the same hydrogen pressure. They represented the first tetraphenylene derivative successively employed in the Rh-catalyzed hydrogenations (Table 2, entries 17−20), especially in the reduction of the methyl α-acetamidocinnamate **1c** (Table 2, entry 20).[24] Catechol-based phosphoramidites **12** are easily prepared and, combined with Rh salts, exhibited relative high ee's (up to 92%), especially the complex **12g**−[Rh], which afforded the optimum hydrogenated products **2**, containing an aryl substituent at the β-position (Table 2, entries 21 and 22).[25] Phosphoramidites (S_a)-**8ad**, (S_a)-**8ae**, (S_a)-**8aj**, (*R*,*R*)-**14a-c**, (S_a)-Monophos (S_a)-**8a**, and (S_a)-H_8-Monophos (S_a)-**13a** were evaluated together as components of the Rh complexes during the hydrogenation of methyl α-acetamidocinnamate. The more simple (S_a)-**13a** was previously reported as the most efficient ligand for this transformation, working under moderate pressure (5 atm), as depicted in entries 23 and 24 of Table 2.[26]

A new spirocyclic diol was isolated by resolution with *N*-benzylcinchonidinium chloride and further transformed into the corresponding phosphoramidite (R_a)-**15**. The (R_a)-**15**−[Rh] complex was successfully applied to the catalytic hydrogenation reaction of methyl α-acetamidoacrylate **1a** and methyl α-acetamidocinnamate **1c**, under 1.7 atm, obtaining excellent enantioselectivities ranging from 98 to >99% ee (Table 2, entries 25 and 26).[27] Continuing with spirocompounds, the spiro-indanyl phosphoramidites (S_a)-**16a** and (S_a)-**16e-g** (Siphos family) also gave good to excellent enantioselectivities under atmospheric pressure of hydrogen in the mentioned hydrogenation reaction[28,29] (up to 99% ee, Table 2, entries 27 and 28), indicating that a faster reaction occurred when the ligand/[Rh] ratio is 1 rather than 2. Based on kinetic studies and X-ray diffraction analysis, which demonstrated the presence of two monodentate ligands in the catalyst, the authors proposed a Rh-catalytic species **20**. The authors suggested that this catalyst loses one ligand, giving species **21**, coordinating 1 equiv of the chiral ligand with 1 equiv of the metal, which is considered as the active catalytic intermediate[29] (Scheme 3).

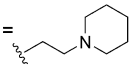
Phosphoramidites containing the *p*-vinylaniline moiety (S_a)-**8y**, or the vinylquinoleine (S_a)-**8as**, were prepared with the aim of copolymerizing them with styrene, affording macromolecules **8at** and **8au**, respectively. The obtained enantioselectivities using these polymeric ligands bonded to a Rh atom were not as high as the examples described before (Table 2, entries 29−32), but an advantage of these polymer-supported catalysts is the easy recovery of the Rh complexes, which can work in four consecutive processes without any loss of activity.[30] In the heterogeneous enantioselective catalysis of bridged phosphoramidites, (S_a)-**8av**−(S_a)-**8ax** were more efficient ligands, operating at higher hydrogen pressure, than the previously cited (S_a)-**8at** and (S_a)-**8au**, generating the corresponding Rh complexation products **2** with ee's ranging from 94 to 97% (Table 2, entries 33−35). After filtration, the metallic catalyst was reused in seven new consecutive reactions with a slight dropping of the enantioselections after the third run but almost constant enantioselection from the fourth to the seventh runs (90−91% ee).[31] The axially chiral backbone derivative (R_a)-**17** was attached to two units of the third-generation carbosilane dendritic wedges, producing dendrimer (R_a)-**18**, which was recovered from the reaction mixture after filtration and reused in several cycles with identical catalytic efficiency. A comparison between Monophos (R_a)-**8a** and related phosphoramidites (R_a)-**17** and (R_a)-**18** (Table 2, entries 1, 36, and 37) as ligands in the Rh-catalyzed enantioselective hydrogenation showed an identical behavior between Monophos (R_a)-**8a** and dendrimer (R_a)-**18** (up to 95% ee) and a lower enantioselection induced by the complex formed from ligand (R_a)-**17**.[32] Efficient immobilization of Rh−Monophos−[Rh] was performed on the aluminosilicate AlTUD-1 (*via* ionic interactions), allowing the recovery of the catalytic complex and leading to the conclusion that its activity is hardly affected by the supporting agent.[33]

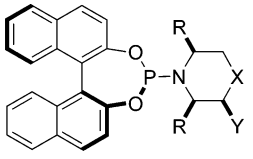
Very recently, the reduction of the C_2 symmetry to C_1 symmetry has been achieved in ligands (S_a,*S*)-**19** with the simultaneous generation of a stereogenic center at the phosphorus atom. The resulting ligands (S_a,*S*)-**19a**−**c**,**d**−**f** induced a very high enantioselection when taking part of the Rh species considered as catalyst in the hydrogenation process of the substrate **1a** at 1.3 atm of hydrogen pressure (Table 2, entries 38 and 39). However, the nonoxygenated arm ligands (S_a,*S*)-**19e**,**k** gave, in general, moderate enantioselectivities for the identical transformation.[34]

In general, phosphite ligands **22**−**25** (Figure 4) are not as effective as phosphoramidites in the Rh-catalyzed enantioselective hydrogenation of substrates **1** (see Table 3) operat-



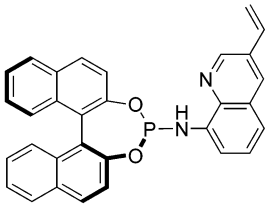
(S_a)-**8**

a; $R^1 = R^2$ = Me (Monophos)
b; $R^1 = R^2$ = Et
c; $R^1 = R^2$ = Pr
d; R^1 = Me, $R^2 = {}^t$Bu
e; R^1 = H, $R^2 = {}^i$Pr
f; R^1 = H, $R^2 = {}^t$Bu
g; R^1 = H, $R^2 = {}^n$Bu
h; R^1 = H, $R^2 = (CH_2)_2{}^t$Bu
i; R^1 = H, $R^2 = (CH_2)_8$Me
j; R^1 = H, R^2 = Cy
k; R^1 = H, R^2 = 1-adamantyl
l; R^1 = H, R^2 = geranyl
m; R^1 = H, R^2 = Bn
n; R^1 = H, R^2 = 
o; R^1 = H, R^2 = 
p; R^1 = H; $R^2 = (CH_2)_2NEt_2$
q; R^1 = H; $R^2 = (CH_2)_2OMe$
r; R^1 = H, $R^2 = CH_2CH(OMe)_2$
s; R^1 = H, $R^2 = CHPh_2$
t; R^1 = H, $R^2 = CH_2$-(1-naphthyl)
u; R^1 = H, $R^2 = CH_2$-(2-pyridyl)
v; R^1 = H, $R^2 = (CH_2)_2$-(2-pyridyl)
w; R^1 = H, R^2 = Ph
x; R^1 = H, R^2 = 2-Et-C_6H_4
y; R^1 = H, R^2 = 4-vinyl-C_6H_4
z; R^1 = H, R^2 = 2-(MeO)C_6H_4
aa; R^1 = H, R^2 = 4-$(NO_2)C_6H_4$
ab; R^1 = H, R^2 = 2-(1,1'-biphenyl)
ac; R^1 = H, R^2 = 2-pyridyl

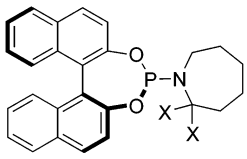


(S_a)-**8**

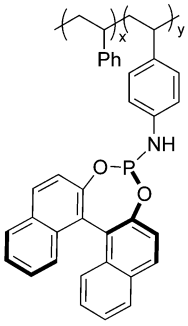
ag; R = Y = H, X = CH_2 (Pipphos)
ah; R = Y = H, X = O (Morfphos)
ai; R = Y = H, X = S
aj; R = Me, X = CH_2, Y = H
ak; R = H, X = CH_2, Y = CO_2Et
al; R = Y = H, X = CH_2CO_2Me
am; R = Y = H, X = NPh



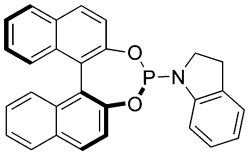
(S_a)-**8as**



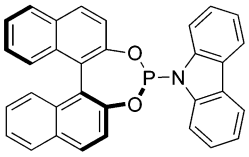
(S_a)-**8**
an; X = H
ao; X = O



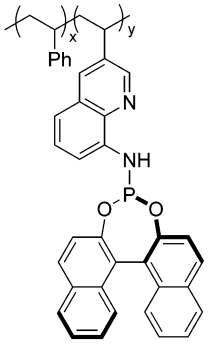
(S_a)-**8at**



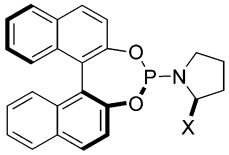
(S_a)-**8ap**



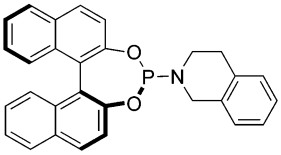
(S_a)-**8aq**



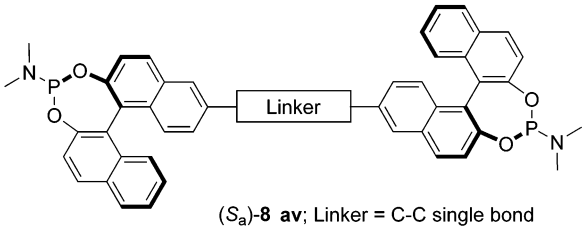
(S_a)-**8au**



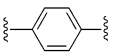
(S_a)-**8**
ad; X = H
ae; X = CO_2Me
af; R = CO_2Bn

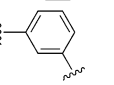


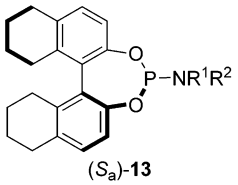
(S_a)-**8ar**



(S_a)-**8** **av**; Linker = C-C single bond

aw; Linker = 

ax; Linker = 



(S_a)-**13**

a; $R^1 = R^2$ = Me (H_8-Monophos)
b; $R^1 = R^2$ = Et
c; R^1–R^2 = –$(CH_2)_5$–
d; R^1–R^2 = –$(CH_2)_6$–
e; R^1–R^2 = –$(CH_2)_2$-N(Ph)-$(CH_2)_2$–

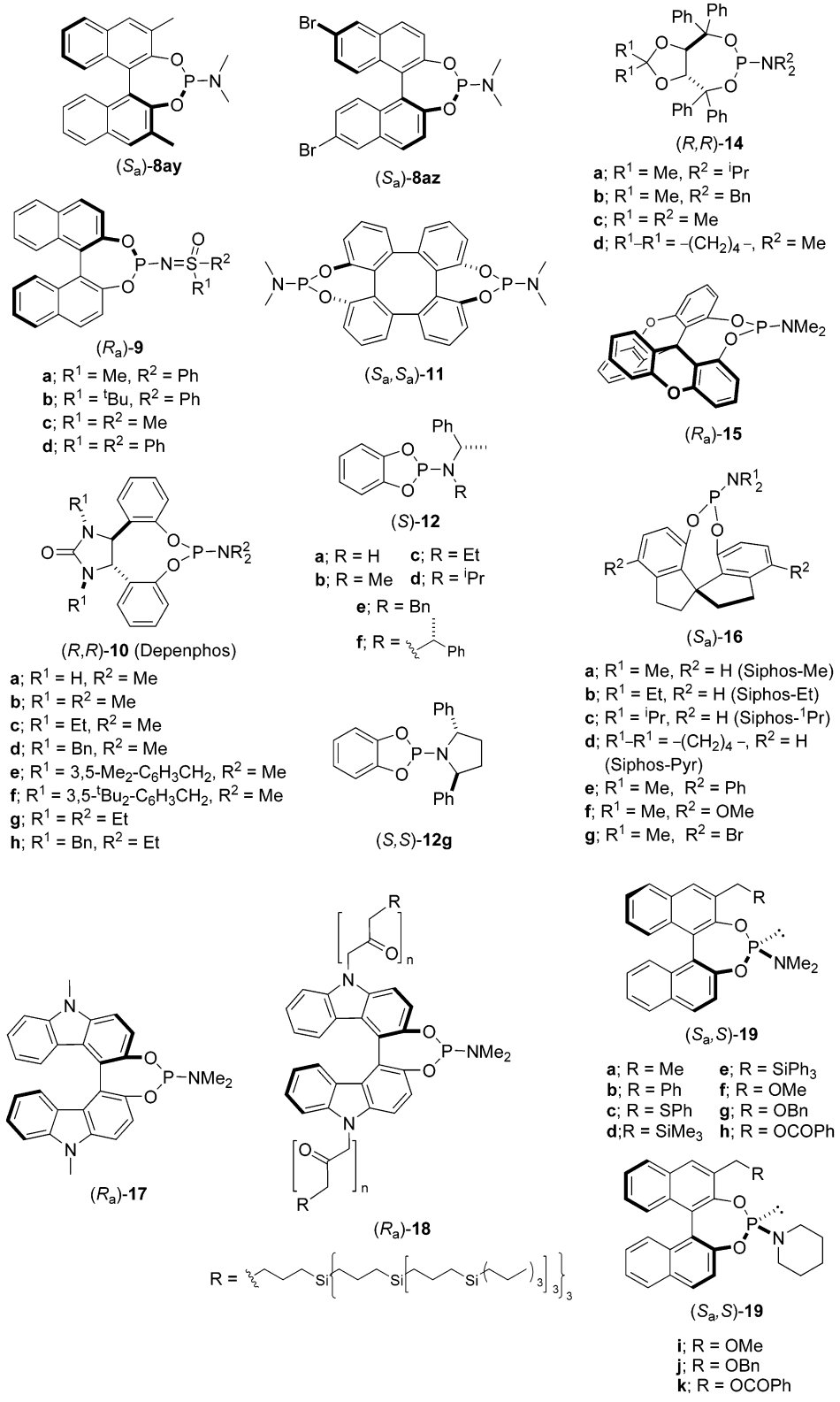


Figure 3. Chiral monodentate phosphoramidite ligands.

ing at very low hydrogen pressures (1−3 atm) (Table 3). The [Rh]−biphenyl backbone of the phosphite (R_a)-**22** complex afforded both good conversions and ee's under mild reaction conditions (Table 3, entry 1).[35] The structure of the ligand (S_a,*R*)-**23** is very similar to C_1-phosphoramidites **19**, but on this occasion, its particular configuration at the phosphorus atom was only able to induce a 97% ee in the hydrogenation of the methyl α-acetamidoacrylate **1a** (Table 3, entry 2).[34]

O-Acyl and *O*-methyl phosphites (R_a)-**24** were easily prepared from the corresponding Binol and immediately coordinated to the Rh atom for studying the carbon−carbon-bond reduction of the acrylate **1a**. The results were very disappointing, obtaining the highest ee when employing (R_a)-**24b**−[Rh] as catalytic complex (Table 3, entry 3).[36] Chiral phosphite ligands **25a**−**g**, composed of D-mannitol and a chiral Binol part (Manniphos ligands), proved to be very interesting donors for the titled enantioselective reduction

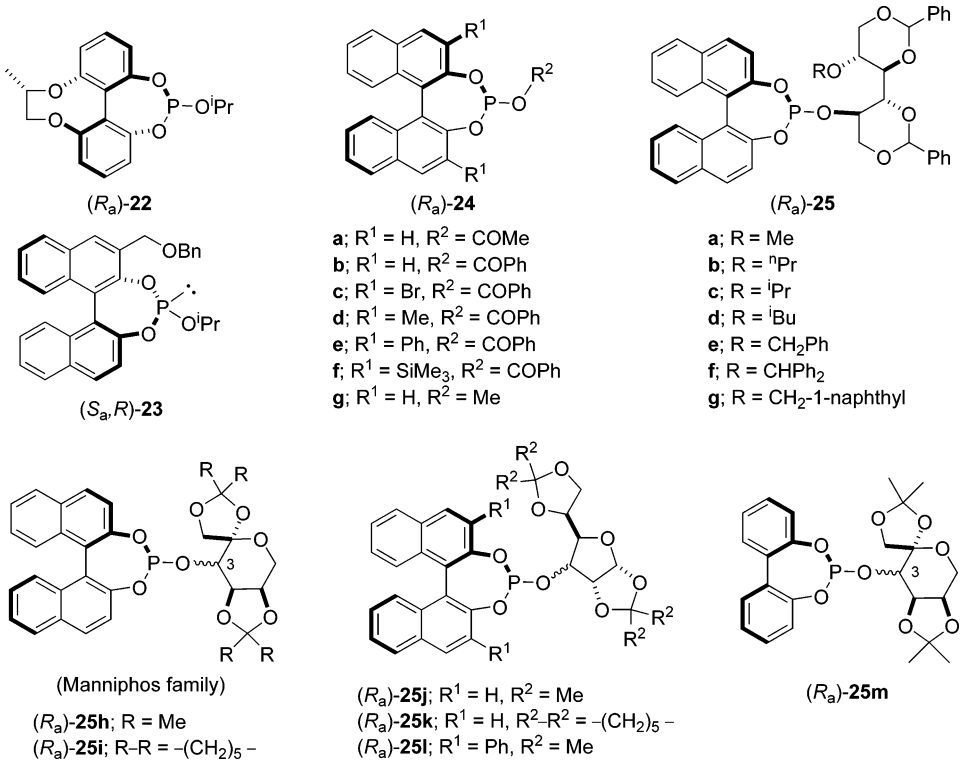
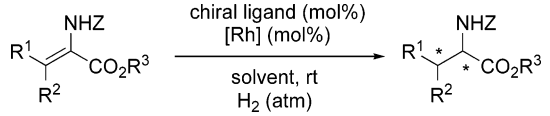


Figure 4. Chiral monodentate phosphite ligands.

Table 3. Enantioselective Synthesis of Compounds 2 Using Phosphite Ligands 22−25 Complexed with [Rh]



			1 (Z = Ac)					product **2**			
entry	ligand (mol %)	[Rh][a] (mol %)	R^1	R^2	R^3	solvent[b]	P_{H_2} (atm)	conv (%)	config	ee (%)	ref
1	(R_a)-**22** (2)	2	H	H	Me	DCM	3	100	(*S*)	93	34
2	(S_a,*R*)-**23** (1)	0.5	H	H	Me	DCM	1.3	100	(*S*)	97	35
3	(R_a)-**24b** (2)	1	Ph	H	Me	PhMe	1	100	(*S*)	75	36
4	(R_a)-**25ag** (2.2)	1	H	H	Me	DCM	1.2	100	(*S*)	94−98	37
5	(R_a)-**25a** (2.2)	1	Ar	H	Me	DCM	1.2	100	(*S*)	97−98	37
6	(R_a)-**25h**[c] (2.2)	1	H	H	Me	DCM	1.2	>99	(*S*)	86	38
7	(R_a)-**25i**[c] (2.2)	1	H	H	Me	DCM	1.2	>99	(*S*)	85	38
8	(R_a)-**25j**[c] (2.2)	1	H	H	Me	DCM	1.2	>99	(*S*)	88	38
9	(R_a)-**25k**[c] (2.2)	1	H	H	Me	DCM	1.2	>99	(*S*)	89	38
10	(R_a)-**25k**[c] (2.2)	1	Ph	H	Me	DCM	1.2	>99	(*S*)	86	38
11	(R_a)-**25k**[c] (2.2)	1	Ar	H	Me	DCM	1.2	>99	(*S*)	80−89	38

[a] [Rh] = $[Rh(cod)_2]BF_4$. [b] Reactions run at 25 °C. [c] (R_a)-Binol.

of DAA derivatives.[37] The range of enantioselection was 94−98% ee, when methyl ester **1a** was the chosen substrate (Table 3, entry 4). The most efficient ligand of this series was (R_a)-**25a**, also employed in the asymmetric hydrogenation of the aryl-substituted α-acetamidoacrylates **1** (Table 3, entry 5). The same group also surveyed other carbohydrate-derived monophosphite ligands, **25h**−**25m**, in this Rh-catalyzed hydrogenation, obtaining the best results for the matched ligands (R_a)-**25h**−**k**, with compounds **2** being obtained with ee's up to 89% (Table 3, entries 6−11).[38]

In many instances, two types of monodentate ligands are combined in equimolar amounts, together with 1 equiv of the Rh salt, affording better enantioselectivities in the hydrogenation reaction than the corresponding one obtained for the same reaction catalyzed by a Rh complex formed by 2 equiv of a unique monodentate ligand. This methodology is relevant whenever the catalytic active species is L_AL_B−[Rh] (derived from the heterocombination of ligands L_A and L_B) in the transition state of the reaction. This complex exists in equilibrium with the other two possible homocombination catalysts, namely L_AL_A−[Rh] and L_BL_B−[Rh]. The first application of this idea was reported by Reetz et al. in the enantioselective catalyzed hydrogenation of methyl α-acetamidoacrylate **1a** in DCM, at room temperature and using 1.3 atm of hydrogen pressure. The best results were obtained by the combinations of phosphonite−phosphonite, **7a**−**7c** and **7a**−**7d**, and phosphonite−phosphite, **7d**−**24g** (up to 98% ee in both examples).[39] In a parallel study, the same group published the combination of chiral and achiral monodentate ligands in the asymmetric Rh-catalyzed hydrogenation of compound **1a**, with reversal of enantioselectivity being possible in some particular

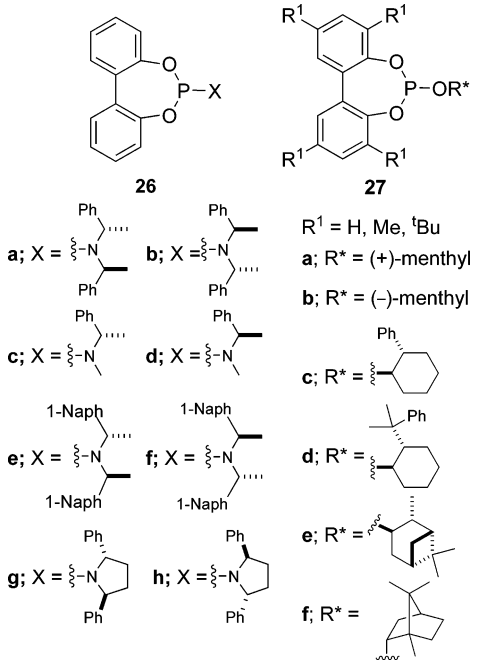


Figure 5. Chiral monodentate biphenol phosphoramidites and phosphites.

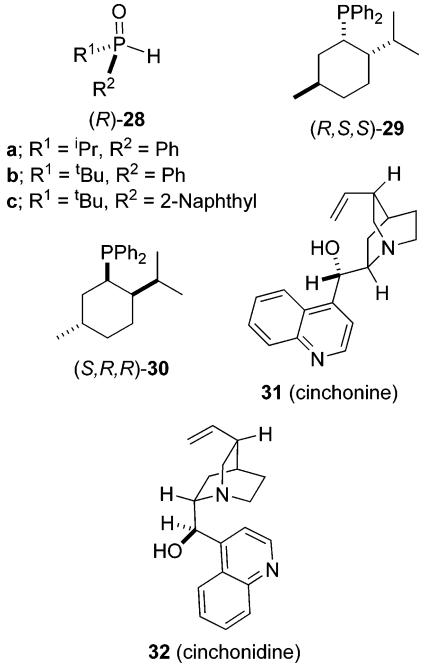


Figure 6. Chiral monodentate ligands for other metal complexes different from Rh.

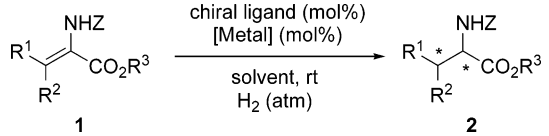
examples. From whole combinations checked in the generation of the active complexes, the couples Monophos **8a** (Figure 3)/triisopropylphosphine and **8a**/tris(2-naphthyl)-phosphine gave 97% ee of the compound (*S*)-**2a**.[40]

A very wide library of chiral tropos−phosphorus ligands containing a biphenyl unit (Figure 5) have been used in analogous hydrogenations of DAAs **1a**−**d**. Many combinations were attempted, with the highest enantioselections being achieved by the **26a**,**27c**−[Rh] (in **26a** with $R^1 = H$). The ee obtained in the reactions performed with compounds **1a**,**b**,**d** (93−95%) contrasted with the 85% ee generated from the starting cinnamate derivative **1c**.[41,42]

2.1.2. Other Transition Metal Chiral Monodentate Ligand Complexes

The Ir complexes have been less applied than the Rh and the Ru ones in the enantioselective catalytic asymmetric hydrogenation of DAAs. Comparisons between Rh (working at $P_{H_2} = 5$ atm) and Ir (working at $P_{H_2} = 10$ atm) complexes have been evaluated by using chiral phosphine oxides **28a**−**c** (Figure 6). Compounds **1a**−**d** were hydrogenated, giving low enantioselections (Table 4, entries 1 and 2). However, branched DAA derivatives such as **1f**−**i** were more suitable substrates for the Ir complexes rather than Rh complexes. Particularly, compound **1i** [$R^1-R^2 = (CH_2)_5$] reacted completely under 10 atm of hydrogen pressure, at room temperature, in the presence of the catalyst formed by [Ir(cod)Cl]$_2$ and the ligand **28b** (Table 4, entries 3 and 4).[43] The two ligands **29** and **30** were used in the formation of the chiral cobalt(II) complexes in the presence of sodium borohydride. The resulting cobalt complexes furnished modest enantioselectivities in compounds **2** (up to 42% ee), operating under very high pressures (60 atm) (Table 4, entries 5 and 6). The inversion of the enantioselectivity in the hydrogenation of methyl α-acetamidocinnamate **1c** has been observed when a *Cinchona*-supported Pd/Al_2O_3 catalyst was employed. In spite of the low enantioselectivities obtained (up to 22% ee) when higher alkaloid concentrations are present in the reaction media, the sense of the enantioselectivity inverted from that of cinchonidine in a different mixture of solvents.[44] In conclusion, the chiral Rh complexes are more suitable than other transition metals for an efficient catalytic enantioselective hydrogenation of DAA derivatives **1**.

Table 4. Monodentate Ligands 28−32 in the Enantioselective Hydrogenation of Alkenes 1 Catalyzed by Metals Different from Rh



			1 (Z = Ac)					product **2**			
entry	ligand (mol %)	metal salt (mol %)	R^1	R^2	R^3	solvent	P_{H_2} (atm)	conv (%)	config	ee (%)	ref
1	(*R*)-**28b** (4)	[Ir(cod)Cl]$_2$ (2)	Ph	H	Me	DCM	5	100	(*S*)	30	43
2	(*R*)-**28b** (4)	[Ir(cod)$_2$]BF_4 (2)	Ph	H	Me	DCM	10	100	(*S*)	29	43
3	(*R*)-**28b** (4)	[Ir(cod)Cl]$_2$ (2)	–$(CH_2)_5$–		Me	DCM	10	100	(*S*)	31	43
4	(*R*)-**28b** (4)	[Ir(cod)$_2$]BF_4 (2)	–$(CH_2)_5$–		Me	DCM	10	100	(*S*)	85	43
5	(*R*,*S*,*S*)-**29** (2)	$CoCl_2$ (1)	Ph	H	Me	PhMe/EtOH	60	61	(*S*)	40	44
6	(*S*,*R*,*R*)-**30** (2)	$CoCl_2$ (1)	Ph	H	Me	PhMe/EtOH	60	78	(*S*)	42	44
7	**32** (10)	Pd/Al_2O_3 (5)	Ph	H	Me	MeOH	3	100	(*S*)	22	45

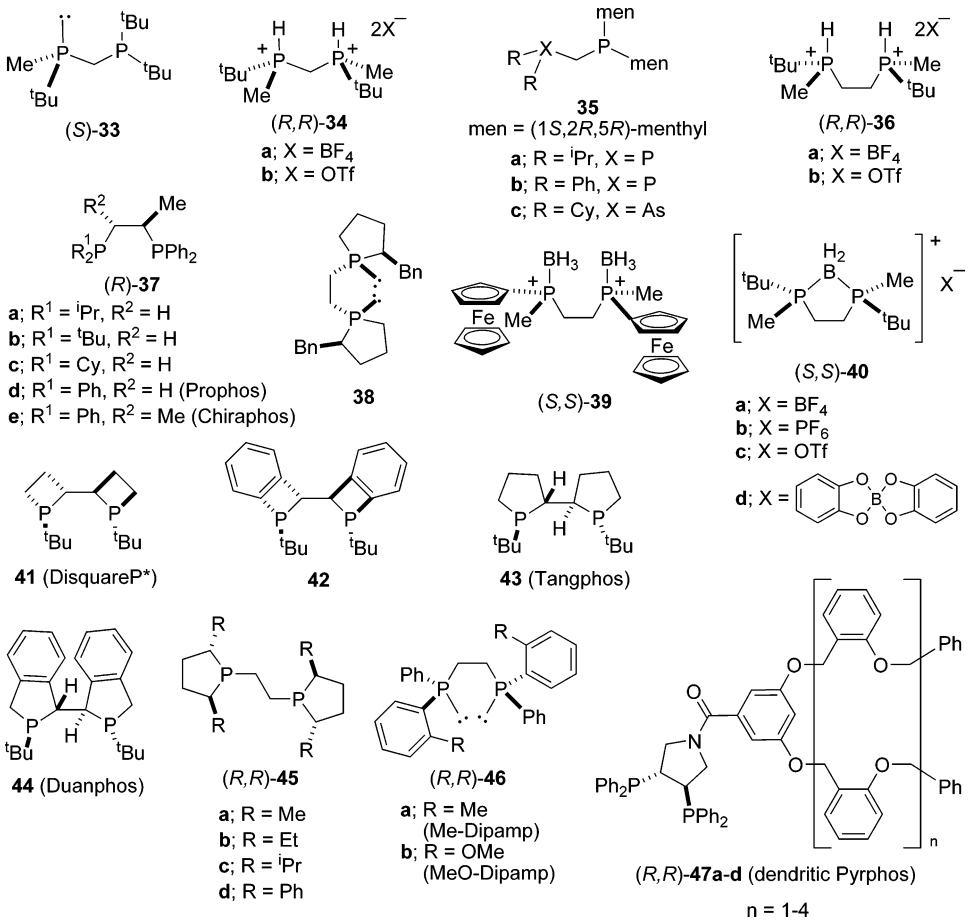


Figure 7. Chiral 1,1- and 1,2-diphosphinoalkanes.

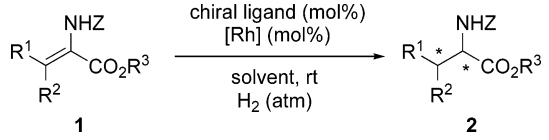
2.1.3. Chiral Bidentate Ligand–Rh Complexes

The results of the enantioselective catalytic hydrogenation mediated by Rh complexes become excellent when a bidentate ligand is coordinated to the metal, rather than monodentate ones, and usually smaller amounts of the ligand are required. The efficiency has been extensively demonstrated.[10h]

Starting from the simplest 1,1-diphosphinomethane (Figure 7), there was reported in the literature a highly selective asymmetric hydrogenation, using a pressure of hydrogen of 3.4 atm, induced by bisphosphine (*S*)-**33**. The authors proposed that the complex ligand **33**−[Rh] possesses three hindered quadrants and one unhindered quadrant, which facilitates the substrate approach exhibiting an excellent enantioselection (Table 5, entries 1−5).[46] Previously to this contribution, ligands with similar structure (*R*,*R*)-**34** were tested, in the presence or in the absence of Brönsted bases, in the analogous reaction with slightly lesser stereoselectivity than the previous examples (Table 5, entry 6),[47] with very disappointing results being achieved with ligands **35** at different temperatures (Table 5, entry 7).[48] 1,2-Bisphosphonium salts (*R*,*R*)-**36**, which are homologous compounds of ligands **34**, gave better enantioselections for the substrates depicted in Table 5[47] (entries 8−10). As well as 1,1-bisphosphines **35**, 1,2-bisphosphines (*R*)-**37** afforded products **2** with low to moderate ee's in the Rh-catalyzed hydrogenations of alkenes **1**.[48] The ligand **38**−[Rh] complex exhibited its best enantioselection with substrate **1a** under 2 atm of hydrogen pressure (Table 5, entry 11), while other α-acetamidoacrylates gave lower ee's (Table 5, entries 12−14).[49] Phosphinoborane adducts **39**[50] and **40**,[51] coordinated to the Rh central atom, did not give such excellent results although, on occasion, drastic reaction conditions were employed (Table 5, entries 15 and 16). On the contrary, DisquareP* **41** was used as a highly efficient ligand in the Rh-catalyzed hydrogenation reaction, furnishing excellent enantioselectivities under an atmospheric pressure of hydrogen (Table 5, entries 17−19).[52] Curiously, a very similar bisphosphine **42** including a benzocondensated ring did not afford good results (Table 5, entry 20).[53] An identical structural relationship exists between Tangphos **43**[54] and its benzocondensated derivative Duanphos **44**,[55] but on this occasion, there was not such a significant gap in enantioselectivities for the catalytic hydrogenation mediated by the corresponding **43**-[Rh] and **44**-[Rh] complexes under 1.4 atm of hydrogen pressure (Table 5, entries 21 and 22). It is noteworthy that high turnover number (TON = 10400) and high turnover frequency (TOF = 5×10^3 h^{-1}) were achieved with the **44**−[Rh] in the hydrogenation of acrylate **1a** at room temperature.[55] The presence of a phenyl substituent in phosphines **45** exhibited the highest enantioselection in the Rh-catalyzed hydrogenation of **1c** *versus* other different substituents (Table 5, entry 23).[56] The conformations of the chelates of norbornadiene and cyclooctadiene complexes of the Dipamp ligand **46** were dramatically different, with the norbornadiene complex being the most efficient (Table 5, entry 24).[57]

The asymmetric hydrogenation of the DOPA precursor **1** (R^1 = Ar, R^2 = H) using Dipamp **46** was investigated, and it was concluded that the minor substrate complex dominated the enantioselectivity of the process, because of its approximately 350-fold higher reactivity compared to the

Table 5. Enantioselective Synthesis of Compounds 2 Using Phosphorus Ligands 33−47 Complexed with [Rh]



1 2

			1 (Z = Ac)					product **2**			
entry	ligand (mol %)	[Rh][a] (mol %)	R^1	R^2	R^3	solvent[b]	P_{H_2} (atm)	conv (%)	config	ee (%)	ref
1	(*S*)-**33** (1)	1	H	H	H	MeOH	3.4	100	(*R*)	>99	46
2	(*S*)-**33** (1)	1	Ph	H	H	MeOH	3.4	100	(*R*)	>99	46
3	(*S*)-**33** (1)	1	H	H	Me	MeOH	3.4	100	(*R*)	>99	46
4	(*S*)-**33** (1)	1	Ph	H	Me	MeOH	3.4	100	(*R*)	>99	46
5	(*S*)-**33** (1)	1	$-(CH_2)_5-$		Me	MeOH	3.4	100	(*R*)	99	46
6	(*R*,*R*)-**34** (1)	1[c]	Ph	H	Me	MeOH	3	>99	(*R*)	97 to >99	47
7	**35a−c** (1)	1[d]	Ph	H	Me	^{i}PrOH[e]	1	100	(*R*) or (*S*)	up to 69	48
8	(*R*,*R*)-**36a** (1)	1	Ph	H	Me	MeOH	3	>99	(*R*)	>99	47
9	(*R*,*R*)-**36a** (1)	1	H	H	Me	MeOH	3	>98	(*R*)	96	47
10	(*R*,*R*)-**36a** (1)	1	$-(CH_2)_5-$		Me	MeOH	3	>99	(*R*)	70	47
11	**38** (1)	1	H	H	Me	MeOH	2	100	(*R*)	95	49
12	**38** (1)	1	H	H	H	MeOH	2	100	(*R*)	86	49
13	**38** (1)	1	Ph	H	Me	MeOH	2	100	(*R*)	84	49
14	**38** (1)	1	Ph	H	H	MeOH	2	100	(*R*)	77	49
15	(*S*,*S*)-**39** (0.55)	0.25[f]	$-(CH_2)_4-$		Me	MeOH[g]	6	>99	(*R*)	77	50
16	(*S*,*S*)-**40** (1)	1	Ph	H	Me	MeOH	2	95	(*R*)	89	51
17	**41** (1)	1	Ph	H	Me	MeOH	1	>99	(*R*)	>99	52
18	**41** (1)	1	Ar	H	Me	MeOH	1	>99	(*R*)	>99	52
19	**41** (1)	1	H	H	Me	MeOH	1	>99	(*R*)	>99	52
20	**42** (1)	1	Ph	H	Me	MeOH	1	>99	(*R*)	>96	53
21	**44** (0.01)	0.01	H	H	Me	MeOH	1.4	100	(*R*)	>99	55
22	**44** (1)	1	Ph	H	Me	MeOH	1.4	100	(*R*)	>99	55
23	(*R*,*R*)-**45d** (0.03)	0.03	Ph	H	Me	MeOH	10	100	(*S*)	99	56
24	(*R*,*R*)-**46a** (1)	1[d]	Ph	H	Me	MeOH	3	100	(*S*)	95	57
25	(*R*,*R*)-**47c,d**[h] (0.5−1)	(0.5−1)[b]	Ph	H	H	PhMe/MeOH	60	94−100	(*S*)	up to 99	59

[a] [Rh] = [Rh(nbd)$_2$]BF$_4$. [b] Reactions run at 25 °C. [c] A substoichiometric amount of base was added. [d] [Rh] = [Rh(nbd)$_2$]PF$_6$. [e] At several temperatures. [f] [Rh] = [Rh(cod)Cl]$_2$. [g] Reaction run at 50 °C. [h] Ligand with n = 3 or 4.

reactivity of the corresponding major diastereomer.[58] Novel dendritic bisphosphines Pyrphos **47** were studied in the title reaction, and a dramatic change was observed in terms of catalytic activity and efficiency on going from generation 3 (n = 3) to generation 4 (n = 4), presumably, depending on the globular structure of each of them (Table 5, entry 25).[59]

Chiral 1,3-diphosphines (Figure 8) (*R*)-**48** and (*S*,*S*)-**49** were studied, under a high pressure of hydrogen (60 atm), in the Rh-catalyzed enantioselective hydrogenation of DAA cinnamic derivative **1c**, studying a wide number of reaction conditions and parameters, obtaining modest to low enantioselectivities of the corresponding compound **2c** (Table 6, entries 1 and 2).[48] Ligand (*S*,*S*)-**50b** (Bdpp) was the most appropriate cocatalyst in the hydrogenation of the methyl β-arylcrylates and their carboxylic acids in very short reaction times (Table 6, entries 3 and 4).[60] Highly active Rh complexes, formed from the ligands (*S*,*S*)-**50a** and (*S*,*S*)-**50b** (Bdpp), have been supported on alumina using phosphotungstic acid as anchoring agent, obtaining enantioselectivities lower than or identical to the corresponding ones achieved using the nonsupported Rh complexes and allowing an easy recovery of the catalyst quantitatively (Table 6, entry 5).[61] In connection with these ligands, (*S*,*S*)-**50a** and sodium dodecylsulfate (SDS) served for evaluating kinetic parameters in the asymmetric hydrogenation of DAA derivative **1c** in the aqueous phase.[62] Very poor results (up to 25% ee) have been obtained with bisphosphines (*R*,*R*)-**51** as chiral ligands in the Rh-catalyzed hydrogenation reaction of **1a** and **1c** at room temperature under 1 atm of hydrogen pressure.[63] Bisphosphines with a pinene core **52** were also tested in the asymmetric reduction of the carbon−carbon double bonds of the alkenes **1a** and **1c**. After the optimization of the reaction conditions, the **52a**−[Rh] and **52c**−[Rh] complexes promoted the hydrogenation of acrylates and cinnamates with the highest enantioselectivity, respectively (Table 6, entries 6 and 7).[64] Chiral 1,4-bisphosphines **53** (also named the Bdpmi family) have been used in the Rh-catalyzed enantioselective hydrogenation of *N*-acetamidocinnamate **1c** and other aryl-substituted DAA derivatives, with compound **53c** being the most efficient ligand, furnishing products **2** with very high enantioselectivities (up to 97% ee) (Table 6, entries 8−10).[65]

Ligands **54** (Caap) were designed for a set of catalytic organometallic transformations, but special interest was focused on the Rh-catalyzed enantioselective hydrogenations, in which a 94% ee was achieved during the reduction of substrate **1c** (Table 6, entry 11).[66] Previously, the analogous ligand **54b** was employed in the same reaction pattern of **1c** in the survey of its kinetic parameters in micellar solutions, demonstrating a different activation energy of the hydrogen insertion step in methanol and in the micellar solution (Table 6, entry 12).[67] The encapsulation of compound (*S*,*S*)-**54b** and further solubilization in a polymer surfactant have been achieved and used in a membrane reactor with promising results in the catalytic asymmetric hydrogenation of DAA derivatives.[68] Along the same line, a series of supported Caap ligands (*S*,*S*)-**55**−**58** have been synthesized in order to induce a successful enantioselection and high yield in the process and, mainly, to recover the unaltered complex, which can be reused in other new reactions. In spite of the better results obtained with ligands (*S*,*S*)-**55**,[66] (*S*,*S*)-**56**,[69] and (*S*,*S*)-**57**[69] (Table 6, entries 13−15), very high TON and TOF values

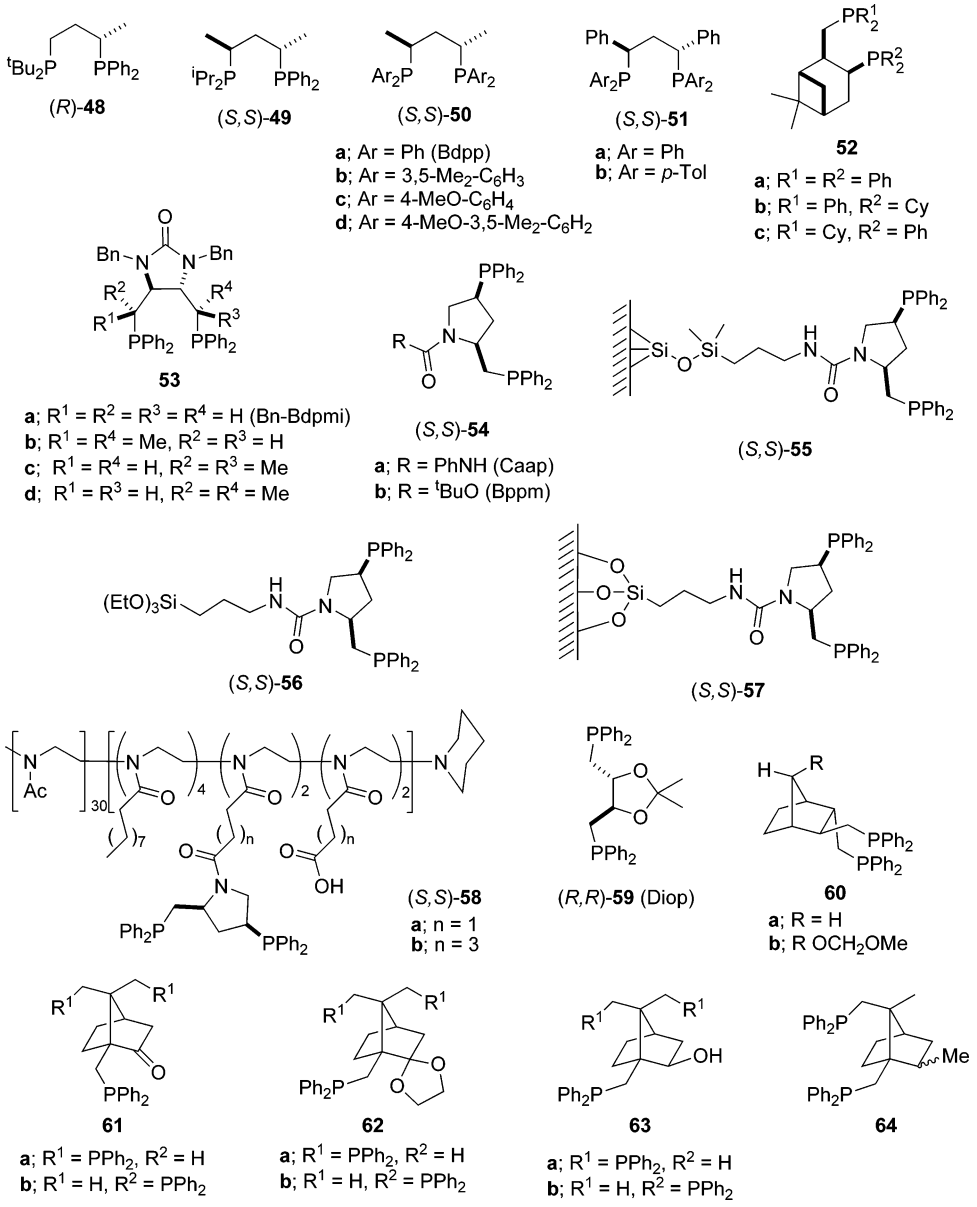


Figure 8. Chiral 1,3- and 1,4-diphosphinoalkanes.

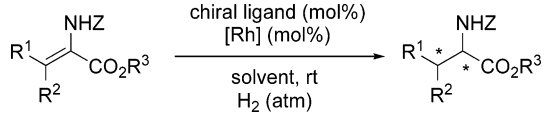
were obtained in the hydrogenation reaction of **1c** employing catalyst (*S,S*)-**58**−[Rh] (Table 6, entry 16).[70]

Ligands **60** were reported in the same work, with the **60a**−[Rh] complex providing the highest enantioselection of hydrogenated compound **2c**[71] (Table 6, entry 17). The following bicyclic bisphosphines **61**−**64** were essayed in the asymmetric hydrogenation of methyl α-acetamidocinnamate **1c** and its corresponding carboxylic acid **1d**. Both ligands **62a** and **63a** (coordinated to the Rh metallic center) gave the most promising results, furnishing ee's up to 88 and 90%, respectively, such as is depicted in entries 18 and 19 of the Table 6.[72] In general, with this series of phosphines, the required hydrogen pressure for obtaining excellent results did not exceeded 2 atm.

Artificial metalloenzymes based on the interaction between biotinylated Rh complexes (Figure 9)[6b] have been studied in enantioselective processes and, especially, in the asymmetric hydrogenation of acrylic acid **1c** and cinnamic acid **1d** derivatives. Initially, bisphosphine **65a** (Figure 10), $[Rh(cod)_2]BF_4$, and streptavidin S122G, in a buffered solution (pH 4.0) at 5 atm of hydrogen pressure and at room temperature, gave compound (*R*)-**2a** in 96% ee.[73] A modification of the spacer by the introduction of a chiral α-AA such as phenylalanine (ligand **65b**) or proline (ligand **65c**) was made. The results of these ligands under the above-mentioned reaction conditions revealed that the proline derivative gave better enantioselections (83−87% and 86−91% ee) when substrates **1b** and **1d** were used.[74] However, the initial studies with **65a** could not be improved in spite of screening multiple structural modifications in the spacer moiety.[75] Following the same concept, the enzyme−Rh complex combination was essayed with a modified Cys-25 papain bonded to a linker with a phosphite terminus and complexed with $Rh(COD)_2BF_4$. The hydrogenation of **1a** has been studied, obtaining complete conversions, although no enantioselectivity was obtained in the final alanine derivative **2a**.[76]

Aromatic 1,2-diphosphines, shown in Figure 11, constituted a very exploited ligand in this particular enantioselective hydrogenation reaction, especially the Duphos family **67**. The absence of the C_2 symmetry between the two phosphorus atoms in ligand (*R,R*)-**66** was judged important in terms of

Table 6. Enantioselective Synthesis of Compounds 2 Using Bishosphine Ligands 48−64 Complexed with [Rh]



1 **2**

			1 (Z = Ac)					product **2**			
entry	ligand (mol %)	[Rh][a] (mol %)	R^1	R^2	R^3	solvent[b]	P_{H_2} (atm)	conv (%)	config	ee (%)	ref
1	(*R*)-**48** (1)	1[c]	Ph	H	Me	^{i}PrOH[d]	1−10	100	(*S*)	up to 20	48
2	(*S*,*S*)-**49** (1)	1[c]	Ph	H	Me	^{i}PrOH	1−10	100	(*S*)	up to 66	48
3	(*S*,*S*)-**50b** (0.5)	0.5[e]	Ar	H	H	MeOH	1	100	(*R*)	up to 98	60
4	(*S*,*S*)-**50b** (0.5)	0.5[e]	Ar	H	Me	MeOH	1	100	(*R*)	up to 97	60
5	(*S*,*S*)-**50b** (2)	2[f]	Ph	H	Me	MeOH	2	70	(*R*)	96	61
6	**52a**−**c** (2.2)	2	H	H	Me	PhMe/MeOH	1	>99	(*R*) or (*S*)	up to 79	64
7	**52a**−**c** (2.2)	2	Ph	H	Me	PhMe/MeOH	1	>99	(*R*) or (*S*)	up to 84	64
8	**53c** (1)	1	Ph	H	H	Me_2CO	1	100	(*R*)	93	65
9	**53c** (1)	1	Ph	H	Me	THF	1	100	(*R*)	95−97	65
10	**53c** (1)	1	Ar	H	Me	THF	1	100	(*R*)	95−97	65
11	(*S*,*S*)-**54a** (1.2)	1[g]	Ph	H	Me	MeOH	2	91	(*R*)	94	66
12	(*S*,*S*)-**54b** (1.5)	1.5	Ph	H	Me	SDS[h]	1	95	(*R*)	93	67
13	(*S*,*S*)-**55** (1.2)	1[i]	Ph	H	Me	MeOH	2	98	(*R*)	93	66
14	(*S*,*S*)-**56** (0.5)	0.5	Ph	H	Me	MeOH	1	>99	(*R*)	94	69
15	(*S*,*S*)-**57** (0.5)	0.5	Ph	H	Me	MeOH	1	>99	(*R*)	94	69
16	(*S*,*S*)-**58a**,**b** (0.03−0.04)	0.03−0.04	Ph	H	Me	micelle	1	94	(*R*)	up to 90	70
17	**60a** (1)	1[j]	Ph	H	Me	EtOH	1	100	(*S*)	80	71
18	**62a** (1)	1	Ph	H	H	DCM	1	100	(*R*)	88	72
19	**63a** (1)	1	Ph	H	H	MeOH	1	100	(*R*)	90	72

[a] [Rh] = $[Rh(cod)_2]BF_4$. [b] Reactions run at 25 °C. [c] [Rh] = $[RhCl(cod)]_2$. [d] Reactions run between −60 °C and rt. [e] [Rh] = $[Rh(nbd)_2]PF_6$. [f] Supported on Al_2O_3. [g] [Rh] = $[Rh(cod)(MeCN)_2]_2$. [h] SDS = sodium dodecylsulfate. [i] [Rh] = $[Rh(cod)(MeCN)_2]BF_4$. [j] $[Rh(nbd)_2]ClO_4$.

the enantioselectivity in the hydrogenation process onto compounds **1a** and **1c** (Table 7, entries 1 and 2).[77] Bidentate Me-Duphos ligand (*R*,*R*)-**67a** formed complexes with Rh salts, which gave very fast quantitative conversions[20] and highly enantioselective hydrogenations. The efficiency of these Duphos ligands **67** was supported by numerous applications in general organic synthesis. For example, the hydrogenation (hydrogen pressure of 2 atm) of cyclobutyl

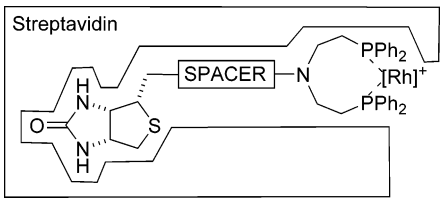


Figure 9. Biotinylated [Rh] complex−streptavidin interaction.

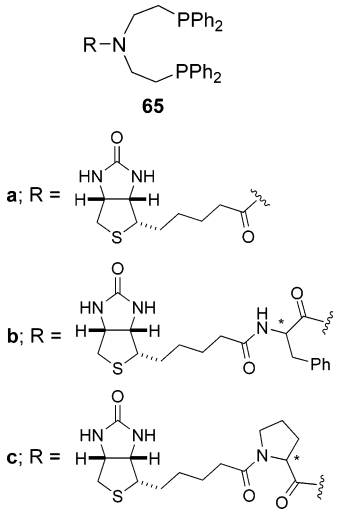


Figure 10. More representative biotinylated 1,5-bisphosphines **65**.

enamides **1j**, **1k**, and **1l** (Figure 12) has been achieved with very high diastereoselectivity, finding in all cases a matched effect between the chiral ligand and the chiral substrate (Table 7, entries 3−7) in the search for new non-proteinogenic constrained α-AAs.[78] DAA derivative **1m** (Figure 12) has been hydrogenated, under 6 atm of hydrogen pressure, with a very good diastereomeric ratio during the course of the synthesis of a precursor of martefragin A (Table 7, entry 8).[79] The same authors completed the asymmetric synthesis of the central tryptophan residue of stephanotic acid, a cyclic peptide isolated from *stephanotis floribunda*, using enantioselective catalytic hydrogenation onto substrates **1n** and *N*-Boc-Ile-**1n**[80] (Figure 12 and Table 7, entries 9 and 10). The synthesis of BILN 2061, a NS3 protease inhibitor with a proven antiviral effect in humans, included the Rh-catalyzed enantioselective hydrogenation of the substrate **1o** (Figure 12), under 6 atm, with Et-Duphos (*S*,*S*)-**67b**.[81] In this transformation, a noticeable chemoselectivity occurred because the terminal alkene remained intact under the reaction conditions detailed in Table 7 (entry 11). An identical situation was observed for the DAA derivatives **1p** and **1q** (Figure 12) during the development of a one-pot hydrogenation−hydroformylation for the preparation of an interesting cyclic α-AA (Table 7, entries 12 and 13).[82] An excellent enantioselectivity (>98% ee) of this process was observed in supercritical carbon dioxide instead of benzene.[82b] Other *β*-branched α-AA derivatives have been constructed through an excellent enantioselective catalysis performed by the complex (*S*,*S*)- or (*R*,*R*)-Et-Duphos **67b**−[Rh], followed by an enzymatic process involving amino acid oxidases (Table 7, entry 14).[83]

Many efforts for the recycling and reusing of the chiral Rh complexes have been made by several groups. The recycling of the (*S*,*S*)-**67b**−[Rh] was achieved by working in ionic liquids (1-butyl-3-methylimidazolium hexafluorophosphate = bmimPF_6) and water. The authors also noticed

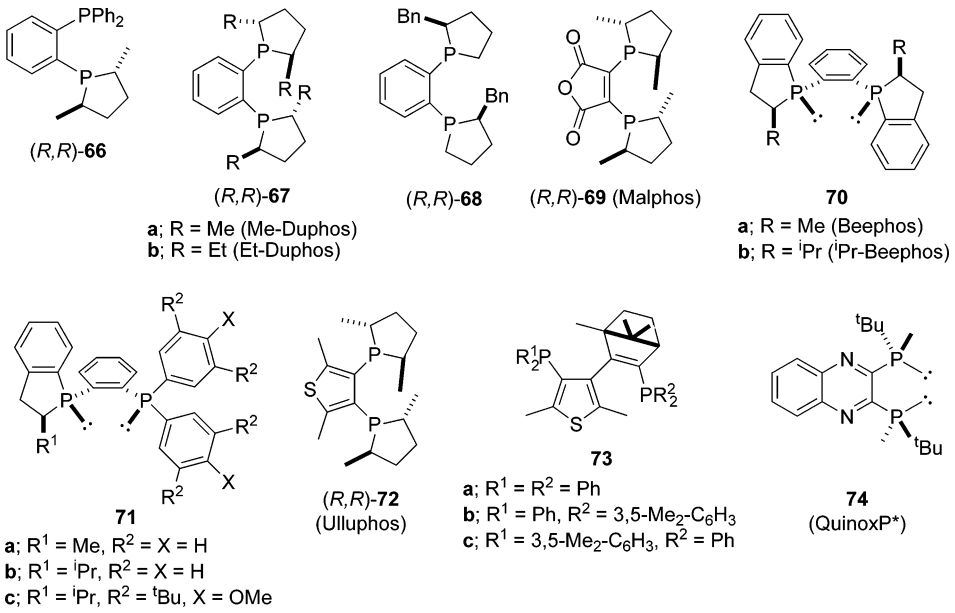
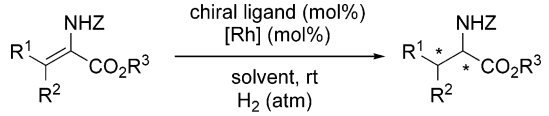


Figure 11. Chiral aromatic 1,2-diphosphines.

Table 7. Enantioselective Synthesis of Compounds 2 Using Bishosphine Ligands 66−74 Complexed with [Rh]



			1 (Z = Ac)					product **2**			
entry	ligand (mol %)	[Rh][a] (mol %)	R^1	R^2	R^3	solvent[b]	P_{H_2} (atm)	conv (%)	config	ee (%)	ref
1	(*R*,*R*)-**66** (1)	1	Ph	H	Me	MeOH	1	100	(*R*)	81	77
2	(*R*,*R*)-**66** (1)	1	H	H	Me	MeOH	1	100	(*R*)	46	77
3	(*R*,*R*)-**67b** (3)	3[c]	(1′*S*,3′*R*)-**1j**			EtOH	2	100	(*R*)	>99.9[d]	78
4	(*R*,*R*)-**67b** (3)	3[c]	(1′*R*,3′*S*)-**1j**			EtOH	2	100	(*R*)	>99.9[d]	78
5	(*R*,*R*)-**67a,b** (3)	3[c]	(1′*R*,3′*R*)-**1k**			EtOH	2	100	(*R*)	up to 80[d]	78
6	(*R*,*R*)-**67a,b** (3)	3[c]	(1′*S*,3′*S*)-**1k**			EtOH	2	100	(*R*)	up to 80[d]	78
7	(*R*,*R*)-**67b** (3)	3[c]	**1l**			EtOH	2	100	(*R*)	74[d]	78
8	(*S*,*S*)-**67b** (0.3)	0.3[c]	**1m**			MeOH	6	>89	(*S*)	>99/1[d]	79
9	(*S*,*S*)-**67b** (0.3)	0.3[c]	**1n**			MeOH	6	98	(*S*)	>99/1[d]	80
10	(*S*,*S*)-**67b** (0.3)	0.3[c]	*N*-Boc-Ile-**1n**			MeOH	6	100	(*S*)	>95/5[d]	80
11	(*S*,*S*)-**67b** (0.1)	0.1[c]	**1o**			EtOH	2	100	(*S*)	>99	81
12	(*S*,*S*)-**67b** (1)	0.1[c]	**1p**			C_6H_6	2−6	100	(*R*)	95−98	82c
13	(*S*,*S*)-**67b** (0.3)	0.3	**1q**			MeOH	5	98	(*S*)	99	82a
14	(*S*,*S*)-**67b** (1)	1	**1r**			MeOH	7	100	(2*S*,3*R*)	>99	83
15	(*S*,*S*)-**67a** (1)	1	**1s**			EtOH/PhMe	10	99	(*S*)	up to 98[d]	86
16	(*R*,*R*)-**68** (1)	1	H	H	Me	MeOH	2	100	(*S*)	98	49
17	(*R*,*R*)-**68** (1)	1	H	H	H	MeOH	2	100	(*S*)	97	49
18	(*R*,*R*)-**68** (1)	1	Ph	H	Me	MeOH	2	100	(*S*)	95	49
19	(*R*,*R*)-**68** (1)	1	Ph	H	H	MeOH	2	100	(*S*)	96	49
20	(*R*,*R*)-**69** (1)	1	Ph	H	Me	THF	1	100	(*R*)	99	91
21	**70b** (0.5)	0.5[c]	Ph	H	Me	MeOH	2	>99	(*R*)	98	92
22	**71** (0.5)	0.5[c]	Ph	H	Me	MeOH	2	>99	(*R*)	up to 73	92
23	(*R*,*R*)-**72** (0.1)	0.1	H	H	Me	MeOH	2.8	100	(*S*)	>99	93
24	(*R*,*R*)-**72** (0.1)	0.1	Ph	H	Me	EtOH	2	100	(*S*)	99	93
25	**73a** (1.1)	1	Ph	H	H	DCM	8	100	(*R*)	>99	94
26	**73a** (1.1)	1	Ph	H	Me	DCM	8	100	(*R*)	>99	94
27	**74** (1)	1	Ph	H	Me	MeOH	3	100	(*R*)	>99	95

[a] [Rh] = $[Rh(nbd)_2]BF_4$. [b] Reactions run at 25 °C. [c] [Rh] = $[Rh(cod)_2]OTf$. [d] >99/1 diastereomeric ratio.

an enhancement of the catalytic activity of these Rh species, presumably ascribed to the creation of a well mixed "emulsionlike" system, and the recycled catalyst was even no longer air sensitive.[84,85] A different strategy for recovering the catalyst has been optimized in a practical route for the synthesis of peptides containing unsaturated α-AAs, where a polymer-supported dehydroalanine system underwent a sequential Pd(0)-catalyzed Mizoroki−Heck reaction/Rh(I)-catalyzed asymmetric hydrogenation reaction. Thus, DAA derivative **1s** (Figure 12) was hydrogenated using (*S*,*S*)-Me-Duphos **67a**, affording excellent de of the supported dipeptide, although employing a relatively high hydrogen pressure (10 atm) (Table 7, entry 15). A new Brönsted acid aluminosilicate AlTUD-1 possessed ideal characteristics for the immobilization of the catalyst (*S*,*S*)-**67a**−[Rh], which was a better catalyst than the analogous **46b**−[Rh] complex

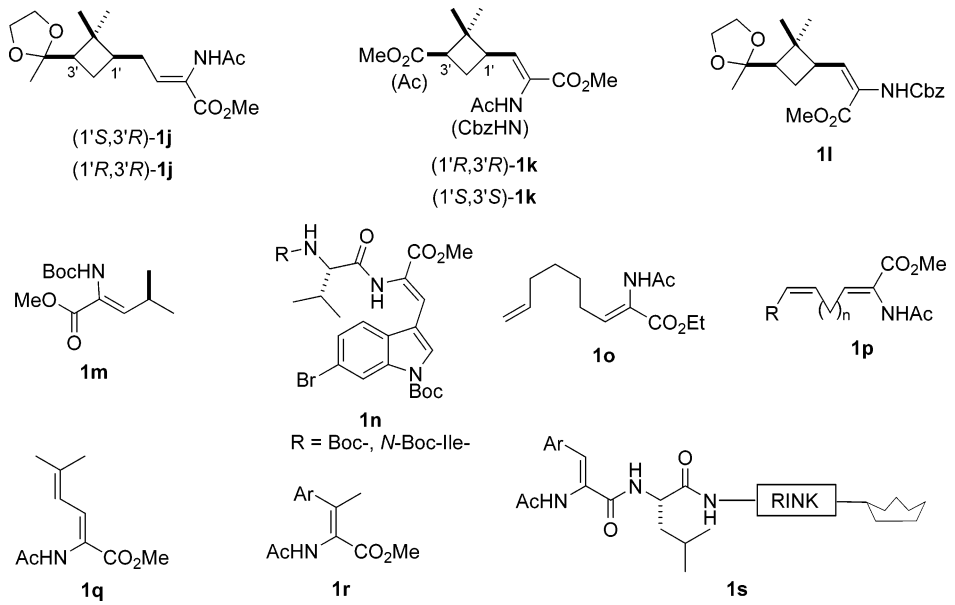


Figure 12. DAA derivatives **1** stereoselectively hydrogenated by Duphos **67**−[Rh].

(Figure 7), obtaining high enantiomeric excesses of the hydrogenated compound **2** (up to 98% ee).[87] The supported catalysts [Rh]−(*S,S*)-**67a**/phosphotungstic acid/Al_2O_3,[88] (*S,S*)-**67a**−[Rh] immobilized by ion exchange into mesoporous aluminosilicate MCM-41,[89] and [Rh]−(*S,S*)-**67a**/aluminated pure silica SBA-15[90] improved the results obtained in the hydrogenations mediated by a large number of ligands (>99% ee for compound **2a**), recovering the unaltered catalyst in all of the previous examples.

Bisphosphine (*R,R*)-**68** (Figure 11) was not as efficient as the Duphos ligand family (*R,R*)-**67** (Figure 11) but also gave higher ee's than ligand **38** (Figure 7) and working under higher hydrogen pressure (compare entries 16−19 of Table 7 with entries 11−14 of Table 5).[49] If we compare the results published in the literature concerning the enantioselective hydrogenations involving ligands (*R,R*)-**69** (Malphos),[91] **70** (Beephos),[92] **71**,[92] and (*R,R*)-**72** (Ulluphos)[93] with the already described data for the reactions mediated by Duphos ligands (*R,R*)-**67**, we can conclude that, using ligands (*R,R*)-**69** (Table 7, entry 20) and, particularly, **70b** (Table 7, entry 21), the enantioselection results were very close to each other. Ligands **70a** and **71** (Table 7, entry 22) offered lower enantioselectivities under identical hydrogen pressure (2 atm). However, Ulluphos ligand (*R,R*)-**72** yielded hydrogenated products **2a** and **2d** with excellent ee's, normally, slightly higher than those obtained using Duphos ligands (*R,R*)-**67** (Table 7, entries 23 and 24) and employing lower catalyst charge, using between 2 and 3 atm of hydrogen pressure.[93] Camphor-derived ligands **73** gave very good results (under 8 atm) in the hydrogenation of the acid **1d** and its methyl ester **1b**, raising, in both cases, more than 99% ee (Table 7, entries 25 and 26).[94] Air stable ligands **74** (QuinoxP*) gave a similar stereochemical outcome to the corresponding one described for the diphosphines **73**, yielding under lower hydrogen pressure compounds **2** with very high ee's (Table 7, entries 27 and 28).[95]

Axial and planar chiral phosphines (Figure 13) have been used with different success in the Rh-catalyzed enantioselective hydrogenation reactions of compounds **1**. Ligands **75**−**78**, which belong to the Biphep family, exhibited interesting chemical behaviors when they were used for the elaboration of the Rh catalytic complex. While bisphosphines (S_a)-**75** and (R_a)-**78** gave very low and moderate enantioselection during the hydrogenation of compound **1a**, ligands (R_a)-**76** and (S_a)-**77** were more effective in this reaction (Table 8, entries 1−4).[96] In a separate previous contribution, (S_a)-*o*-Ph-MeO-Biphep **77** showed extraordinary stereoselectivities for acrylic and cinnamic esters and acids **1a**−**1d** (Table 8, entries 5−8).[97] A new approach for a better understanding of the positioning of the enantio-determining groups in C_2-symmetry was based on the use of new templates to position the carbon atoms in ligands at various coordinates during an asymmetric hydrogenation of enamides **1**. This theory was developed when bisphosphine ligand (S_a)-**79** was allowed to form the Rh complexes in the hydrogenation reaction of **1c**, with **79**c and **79d** being the most efficient chiral entities.[98] The chiral polysubstituted biphenyls **80**[99] and **81**[100] and the 3,3′-bipyridines **82**[101,102] afforded good results of the hydrogenated compounds **2** (Table 8, entries 11−16) but never gave the excellent performance of the homogeneous complex (S_a)-**83**−[Rh] (Table 8, entry 17).[103] Even the (S_a)-**83**−[Rh] complex anchored on a lithiated DOWEX 50W X2 resin was able to maintain a 99.9% ee in its second cycle of the hydrogenation of compound **1a** (Table 8, entry 18),[103] unlike the two silica gel supported Rh complexes derived from bisphosphines (R_a)-**84** and (S_a)-**85**, which induced lower enantioselections during similar transformations[104] (up to 40% ee). The very poor results achieved with the perfluorinated chiral bisphosphine (R_a)-**86**−[Rh] complex[105] are not comparable with those obtained in the corresponding catalytic hydrogenation of **1a** using ligands (S_a)-**87b**−**e** (Table 8, entries 19 and 20).[106] Paracyclophane phosphines (Phanephos) (S_p)-**88a** and (S_p)-**89a**−**d** (Table 8, entries 21 and 22) gave high enantioselectivities, but especially interesting was the example of the (S_a)-**89a**-[Rh] complex, whose TON was the most elevated of this series of chiral ligands.[107] The supported version of these planar bisphosphines as (S_p)-**88b**, grafted onto basic carbons, provided compounds **2a** with ee's up to 97% (Table 8, entry 23).[108] An important feature of these ligands shown in Figure 13 is the relatively low hydrogen pressure of hydrogen (1−5.5 atm) except in the example run with ligand (R_a)-**80b**, where a pressure of 10 atm was employed (Table 8).

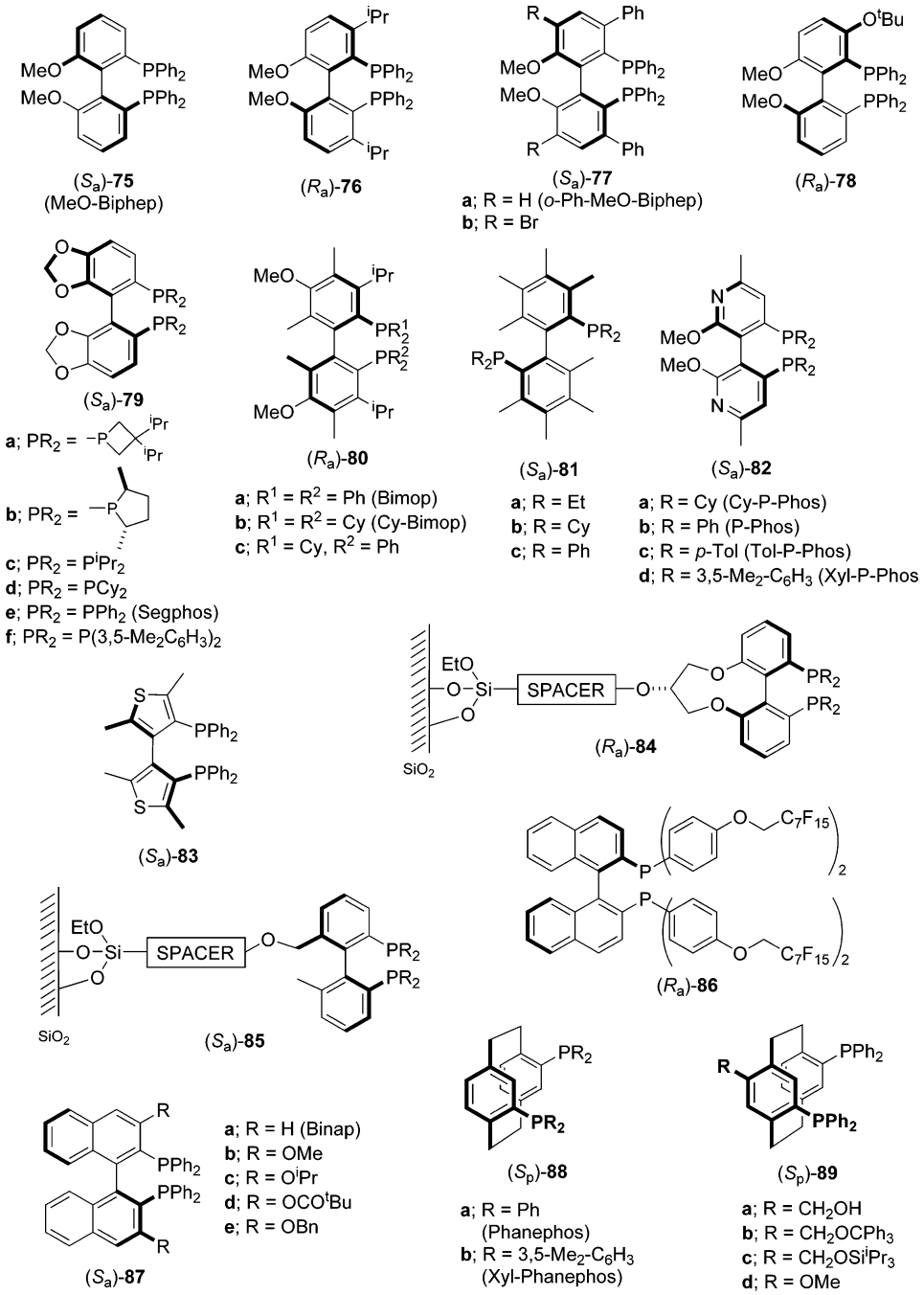
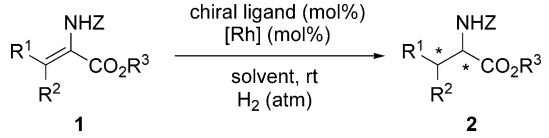


Figure 13. Disphosphines **75**−**89** with axial and planar chirality.

Transition metal-containing planar chiral bisphosphines have also been exploited as ligands in the Rh-catalyzed enantioselective hydrogenation[10h] (Figure 14). Cr-tricarbonyl complexes **90**, also known as Daniphos-type ligands, gave, in general, lower enantioselectivities than ligand Josiphos **97e**, with the exception of monometallic Cr species **90c**.[109] This was the unique ligand able to improve the results reported for the same reaction performed with **97e**−[Rh] (Table 9, entry 1). The same group tested a Daniphos derivative ligand library and obtained some interesting results, such as, for example, **90g**, **90e**, and **90f** (Table 9, entries 2 and 3).[110] Bisphosphines **91**[111] and **92**[110,112] gave similar low to modest enantioselections in the Rh-catalyzed hydrogenation of methyl α-acetamidocinnamate **1c** (Table 9, entries 4 and 5). Thus, it can be concluded that ligands **91** and **92** are not good candidates to develop this type of reactions, except **92c**, which gave more than 70% ee in both series of reactions essayed (Table 9, entry 5).[112] Both ferrocenyl−Rh complexes of Taniaphos **93c** (first generation ligand) and **93d** (second generation ligand) offered the best results in the hydrogenation reaction of alkene **1c** compared to different complexes formed with other Taniaphos derivatives (Table 9, entries 6 and 7).[113] Ligand **94c**, coordinated to Rh metal, generated a catalytic complex that afforded a 95% ee of the saturated compound **2c** (Table 9, entry 8), rather than Walphos **94d**, which induced in this process a 90% ee.[114] Bisphosphine **95** was compared in the same reduction reaction with the ligand (*R*,*R*)-**66** (Figure 11), furnishing ee up to 55% versus the 81% ee obtained by the employment of the latter ligand (Table 7, entry 1).[77] Bisphosphinoferrocenes **96** (Ferrotane) gave notable enantioselections when the methyl group was bonded to the

Table 8. Enantioselective Synthesis of Compounds 2 Using Bishosphine Ligands 75−89 Complexed with [Rh]



1 2

			1 (Z = Ac)					product **2**			
entry	ligand (mol %)	[Rh][a] (mol %)	R^1	R^2	R^3	solvent[b]	P_{H_2} (atm)	conv (%)	config	ee (%)	ref
1	(R_a)-**76** (1.1)	1	H	H	H	MeOH	2	100	(*R*)	98	96
2	(R_a)-**76** (1.1)	1	H	H	Me	MeOH	2	100	(*R*)	95	96
3	(R_a)-**77** (1.1)	1	H	H	H	MeOH	2	77	(*R*)	97	96
4	(R_a)-**77** (1.1)	1	H	H	H	MeOH	2	100	(*R*)	99	96
5	(S_a)-**77** (1.1)	1[c]	H	H	Me	DCM	1.7	>99	(*S*)	>99	97
6	(S_a)-**77** (1.1)	1[c]	H	H	H	DCM	1.7	>99	(*S*)	>99	97
7	(S_a)-**77** (1.1)	1[c]	Ar	H	Me	DCM	1.7	>99	(*S*)	97 to >99	97
8	(S_a)-**77** (1.1)	1[c]	Ar	H	H	DCM	1.7	>99	(*S*)	96 to >99	97
9	(S_a)-**79c** (0.5)	0.5	Ph	H	Me	THF[d]	1	>99	(*R*)	98	98
10	(S_a)-**79d** (0.5)	0.5	Ph	H	Me	THF[d]	1	>99	(*R*)	98	98
11	(R_a)-**80b** (0.2)	0.2[e]	Ph	H	Me	MeOH[f]	10	100	(*S*)	79	99
12	(S_a)-**81a** (0.5)	0.5	Ph	H	Me	MeOH[f]	3	100	(*S*)	88	100
13	(S_a)-**81c** (0.5)	0.5	Ph	H	Me	MeOH[g]	3	100	(*S*)	89	100
14	(S_a)-**82a** (1)	1[h]	Ar	H	Me	Me_2CO[i]	1	>99	(*R*)	up to 97	102
15	(R_a)-**82d** (1)	1[h]	Ph	H	H	MeOH	1	100	(*R*)	91	101
16	(R_a)-**82d** (1)	1[h]	Ar	H	Me	MeOH	1	100	(*R*)	90−94	101
17	(S_a)-**83** (1)	1[j]	H	H	Me	MeOH	5	100	(*S*)	>99	103
18	(S_a)-**83** (1)	1[k]	H	H	Me	MeOH	5	100	(*S*)	>99	103
19	(S_a)-**87b**−**e** (1.1)	1	H	H	H	MeOH	2	100	(*S*)	95 to >99	106
20	(S_a)-**87b**−**e** (1.1)	1	H	H	Me	MeOH	2	100	(*S*)	97 to >99	106
21	(S_p)-**88a** (0.02)	0.02[l]	H	H	Me	MeOH	5.5	100	(*R*)	97	107
22	(S_p)-**89a**−**d** (0.02)	0.02[l]	H	H	Me	MeOH	5.5	100	(*R*)	95−97	107
23	(S_p)-**88b** (1)	1[l,m]	H	H	Me	MeOH	4	100	(*R*)	97	108

[a] [Rh] = $[Rh(cod)_2]OTf$. [b] Reactions run at 25 °C. [c] [Rh] = $[Rh(nbd)_2]SbF_6$. [d] Reaction run at 30 °C. [e] [Rh] = $[Rh(nbd)_2]ClO_4$. [f] Reaction run at 50 °C. [g] Reaction run at −40 °C. [h] [Rh] = $[Rh(cod)_2]BF_4$. [i] Reaction run at 0 °C. [j] [Rh] = $[Rh(nbd)_2]PF_6$. [k] Anchored on a lithiated-DOWEX 50WX2 resin. [l] [Rh] = $[Rh(nbd)_2]BF_4$. [m] Anchored on Acticarbone 2S.

stereogenic center (Table 9, entry 9).[115] In this work, the effect of the ligand 1,2-bis[(*S*,*S*)-2,4-dicyclohexyl-1-phosphetanyl]ethane was also studied, and a clearly lower ee (up to 83%) was obtained. Mandiphos family ligands **98** provided excellent results in the hydrogenations of several unsaturated α-amido esters or acids (Table 9, entries 10−12). It was noticeable that an elevated TON achieved with 5×10^{-3} mol % of the complex **98b**−[Rh] in the reduction of substrate **1c** (99% ee). However, Taniaphos **93c** gave a 93% ee of the hydrogenated compound **2c** with lower TON (Table 9, entry 13).[116] Josiphos **97e** was selected as a reference ligand and resulted to be a more efficient chelate for the Rh atom than ferrocenes **99**, although **99b** afforded a very good ee at 70 °C (Table 9, entry 14).[117] Analogously, Trap-H ligands **100c** gave disappointing enantioselectivities (up to 45% ee) if compared with the enantioselectivities obtained by their precursors Trap ligands **100a** and **b** (up to 96% ee).[118]

A screening of ligands such as ferrocenyl bisphosphines, 1,2- and 1,4-diphosphinoalkanes, and aromatic 1,2-diphosphines (Figures 7, 8, 11, and 14), under several reaction conditions, was carried out in a Rh-catalyzed hydrogenation run in a novel multiphase system consisting of an ionic liquid and water.[119] The most promising results with respect to catalytic performance and catalyst separation and recycling corresponded to the reactions mediated by ferrocenyl bisphosphine−[Rh] catalysts allowing TON > 10^4, which can be industrially relevant.

Cyrhetrenyl diphosphine **101** (Aaphos) (Figure 14) is an uncommon Re complex useful in the Re-catalyzed enantioselective hydrogenation of substrates **1c** and **1d** (Scheme 2), which were selectively reduced under different reaction conditions, affording good to high enantioselections of compounds **2** (Table 9, entries 15 and 16).[120] The last two examples were performed under 5 and 10 atm of hydrogen pressure while the previous better examples, recorded in Table 9, were run under lower pressures ranging from 1 to 1.5 atm.

Perhaps homobidentate ligands **102**−**115** (Figure 15) did not afford such outstanding results as some examples described previously, but they can be used in most cases at atmospheric pressure of hydrogen (Table 10). According to the success of monodentate phosphoramidites described before, bisphosphoramidites **102** and **103** were essayed in the Rh-catalyzed enantioselective hydrogenation of methyl 2-acetamidocinnamate **1c**.[25,26] The ee's of the hydrogenated product **2c** were not as excellent as was initially expected; the **102c**−[Rh] complex was the most effective, affording 36% ee (Table 10, entry 1).[25,26] The new chiral bisphosphoramidites SpiroNP **104** were easily accessible in a short path synthesis. The **104**−[Rh] complex was found to be an excellent catalyst for the synthesis of chiral α-AA derivatives **2** under mild reaction conditions (Table 10, entries 2−5).[121] The more sophisticated bis(iminophosphoranyl)ferrocenes **105** were also suitable ligands for this process; in particular, the **105a**−[Rh] and **105b**−[Rh] complexes gave the best ee's using substrates **1c** and **1a**, respectively (Table 10, entries 6 and 7).[122] Bisphosphinites (S_a)-**106** and its H_8 derivative (S_a)-**107** were compared as ligands of the Rh atom in the hydrogenation of the cinnamate derivative **1c**.[123] The (S_a)-**107**−[Rh] complex gave better enantioselections than the totally aromatic ligand (S_a)-**106**−[Rh] complex, with the H_8-Binol derivative **107f** being the most active ligand bonded to the Rh atom (Table 10, entry 8). The bisphosphinite ligand **108**, incorporating a double 7-phosphanorbornane structure,

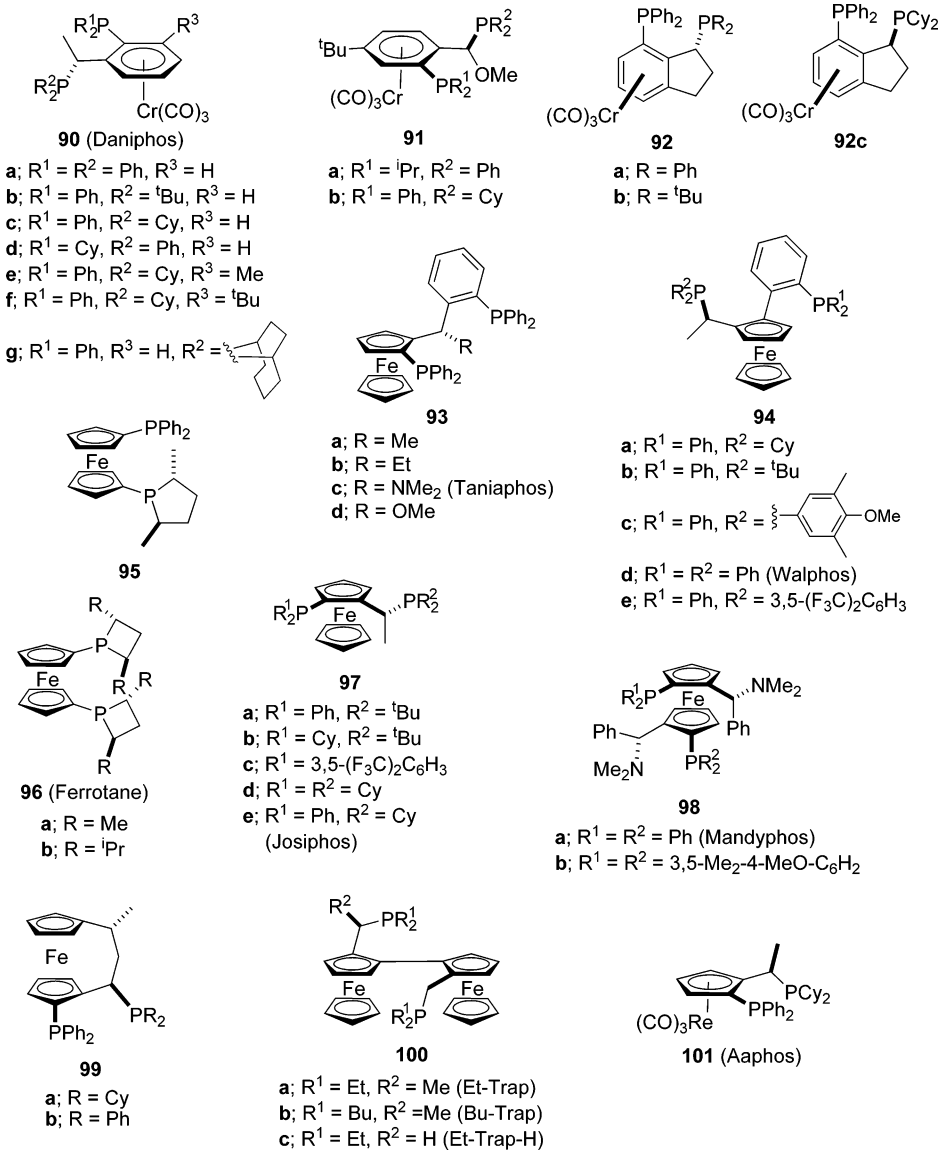


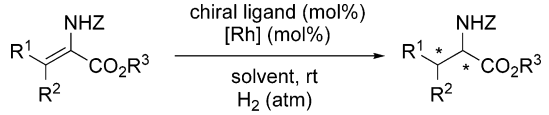
Figure 14. Metalated diphosphines with planar chirality.

was also an efficient ligand for this purpose. Thus, methyl acetamidocinnamate **1c** was hydrogenated with a 94% ee (Table 10, entry 9).[124] Other bisphosphinites **109**−**111**, derived from carbohydrates, are promising structures due to the strong influence exhibited by the remote stereocenters in the asymmetric Rh-catalyzed hydrogenation. The **109e**−[Rh] complex was noticeably more efficient in all of the tested reactions than the other **109**−**111**-derived Rh complexes (Table 10, entries 10 and 11).[125] Concerning these phosphinite ligands and some polyhydroxylated derivatives, the prospects, benefits, and problems of their uses as water-soluble ligands were revised.[126] In spite of the encouraging results obtained with the ligand **112** (Xantbino) in other asymmetric transformations, the Rh-catalyzed hydrogenation of methyl acetamidocinnamate **1c** only afforded a 54% ee in good conversions.[127]

Binol- and H_8-Binol-derived bisphosphites **113** and **114** gave low enantioselection (up to 48% ee) in the Rh-catalyzed hydrogenation of **1c**.[128] However, the ligand **115**, combining two (S_a)-Binol units bonded to a molecule of L-tartaric acid, formed a Rh complex able to promote the hydrogenation of substrate **1c** in 91% ee[129] (Table 10, entry 12).

Heterobidentate ligands **116**−**140** (Figure 16) were especially designed for the enantioselective hydrogenations of olefins and, particularly, for the hydrogenation of DAAs derivatives, finding impressive results in some particular examples performed under high pressures of hydrogen (20−30 atm) (Table 11). The carbene ligand **116**−[Rh] afforded excellent enantioselectivities in the hydrogenation reaction of compounds **1a** and **1c** (Table 11, entries 1 and 2).[130] Numerous tests of the catalytic hydrogenations onto substrates **1** have been described using Bophoz ligands **117a**−**e**.[131−134] In general, all of these gave very satisfactory results, but the aminophosphine−phosphine **117b**−[Rh] complex was the most efficient ligand working under a pressure of hydrogen of 0.7 atm (Table 11, entries 3−6)[131−134] for the whole number of essayed substrates. *N*-Boc, *N*-Cbz, and *N*-acetyl DAA derivatives afforded similar results of the α-AA precursors **2** employing the same catalytic system. During the comprehensive study of the optimization of these reactions, a TON of 30500 and a TOF of 68100 were determined in the hydrogenation of **1c**.[132,134] (*S*)-Cyclopropylalanine was prepared in >99% ee using this **117b**−[Rh] complex as catalyst, rather than complexes derived from **97**

Table 9. Enantioselective Synthesis of Compounds 2 Using Bishosphine Ligands 90−101 Complexed with [Rh]



1 **2**

			1 (Z = Ac)					product **2**			
entry	ligand (mol %)	[Rh][a] (mol %)	R^1	R^2	R^3	solvent[b]	P_{H_2} (atm)	conv (%)	config	ee (%)	ref
1	**90a**−**d** (1)	1	Ph	H	Me	MeOH	1	100	(*R*)	up to 82	109
2	**90e**,**f** (1)	1	H	H	Me	MeOH	1	100	(*S*)	up to 91	110
3	**90g** (1)	1	Ph	H	Me	MeOH	1	100	(*S*)	87	110
4	**91a**,**b** (1)	1[c]	Ph	H	Me	MeOH	5	100	(*R*)	up to 69	111
5	**92c** (1.1)	1	Ph	H	Me	THF	1.5	100	(*S*)	88	112
6	**93c** (1.1)	1[c]	Ph	H	Me	MeOH/MePh	1	100	(*R*)	95	113
7	**93d** (1)	1[c]	Ph	H	Me	MeOH/MePh	1	100	(*S*)	99	113
8	**94c** (0.55)	0.5	Ph	H	Me	MeOH	1	>99	(*R*)	95	114
9	**96a** (1)	1[d]	Ph	H	Me	MeOH[e]	1	>99	(*R*)	96	115
10	**98b** (5×10^{-3})	5×10^{-3}	Ph	H	Me	MeOH	1	>99	(*R*)	99	116
11	**98b** (0.5)	0.5	Ph	H	H	MeOH	5	>99	(*R*)	95	116
12	**98b** (0.5)	0.5	H	H	Me	MeOH	1	>99	(*R*)	95	116
13	**93c** (0.5)	0.5	Ph	H	Me	MeOH	1	>99	(*R*)	98	116
14	**99b** (1)	1[c]	Ph	H	Me	MeOH[f]	1.2	100	(*R*)	95	117
15	**101** (1.5)	1.5[c]	Ph	H	H	MeOH	5	88	(*R*)	89	120
16	**101** (1.5)	1.5[c]	Ph	H	Me	MeOH	10	100	(*R*)	70	120

[a] [Rh] = $[Rh(nbd)_2]BF_4$. [b] Reactions run at 25 °C. [c] [Rh] = $[Rh(cod)_2]BF_4$. [d] [Rh] = $[Rh(cod)_2]OTf$. [e] Reaction run at 50 °C. [f] Reaction run at 70 °C.

or **67a**,**b** ligands (Table 11, entry 6).[131] In addition, a library of these ligands **117** (Bophoz) has been developed testing different substrates.[133] Heterobidentate ligand **118** (Duphamin)[135] gave poor enantioselectivities when it was used in the formation of the Rh complex, while **120**−[Rh] complexes afforded enantioselections up to 74% ee, and the equivalent **119**−[Rh] gave excellent conversions and ee's working under atmospheric pressure of hydrogen (Table 11, entries 7 and 8).[122]

Phosphoramidite−phosphines **121** and **122** offered different behaviors in spite of the equivalent skeleton. **121**−[Rh] and **122a**−**c**−[Rh] aggregates gave ee up to >99% in DCM as solvent, and the **122d**−[Rh] complex was a mismatched combination for this type of transformation (Table 11, entries 9 and 10).[136,137] In these contributions, a triple combination was evaluated, that means, phosphine−phosphinite ligand **123**, phosphine−phosphite ligand **125**, and phosphine−phosphoramidite ligand **124**. Except for the **125**−[Rh] complex, which afforded low ee's of products **2**, Rh complexes of **123b** and **124** offered the highest enantioselections under 10 and 20 atm of hydrogen pressure, respectively.[138] Curiously, the Rh complexes generated from ligands **126** and **127** exhibited identical behaviors and no differences, regarding conversions and enantioselections, were observed when working at atmospheric pressure (Table 11, entries 13−15).[139] The very simple phosphine−phosphinite ligand **128** formed a Rh complex whose activity in the hydrogenation reaction of **1a** and **1c** was checked. The best enantioselections (91% ee) were achieved under a deficient conversion of compound **1a** and in a complete conversion in the case of the starting material **1c**.[140] Ligands **129**, **130**, and **132** cannot be considered as appropriate ligands for the current chemical modification due to their very low enantiodiscrimination.[141,142] Sensibly higher ee's were originated by the combination of $[Rh(cod)_2]BF_4$ with the ligand **131**, hardly raising the 91% ee.[142] The P,S-heterobidentate ligands are considered as good donor ligands for multiple transition metals such as, for example, Rh.[143−148] From the series shown in Figure 16, ligands **133**,[143] **134**,[143] and **139**[147] were not suitable for a selective hydrogenation of DAA derivatives **1**. In contrast, **135**−[Rh] and **136**−[Rh] complexes showed parallel results in the hydrogenations of a large series of unsaturated esters and acids (Table 11, entries 17 and 18), achieving also compounds **2f** and **2i** with 93% and 95% ee, respectively.[144] In this work, the model proposed for the hydrogenation involved a regioselective binding of the substrate determined by the difference of the phosphorus and sulfur donors and the final induction of the newly formed sulfur stereocenter.[144] The complex **137b**−[Rh] was the most important catalyst of these groups of P,S-bidentate ligands but working at 30 atm of hydrogen pressure (Table 11, entries 19 and 20), with the rest of the examples reported being less efficient (up to 68% ee).[145] The ligand **138** has been utilized exclusively in the synthesis of (*S*)-acetamido phenylalanine in 92% ee under 40 atm of pressure (Table 11, entry 21).[146] Bissulfone ligand **140** provided the *N*-acetylalanine methyl ester **2a** in 93% ee performing the reaction under 3 atm of hydrogen pressure (Table 11, entry 22), unlike the results obtained from the chiral sulfoxide, direct precursors of the named sulfones.[148] Finally, all types of ligands introduced in the previous sections have been screened in the Rh-catalyzed hydrogenation of methyl (*Z*)-2-acetamidocinnamate (**1c**) in a gas−liquid and gas−liquid−solid catalysis in a mesh microreactor employing chiral ligand inventory down to 10 nmol, with its application for the kinetic data acquisition also being demonstrated.[149]

2.1.4. Other Chiral Bidentate Ligand–Transition Metal Complexes

It is very unusual to find in the literature a transition metal, different from Rh, able to catalyze enantioselective hydrogenations of DAA derivatives **1**.[10] In some selected cases, Ru and Ir complexes of ligands detailed in Figure 17 furnished enantioselectivities with ee values higher than 95% working with different hydrogen pressures (1−50 atm) (Table 12). The (R_a)-**141** (Synphos) ligand formed Ru complexes

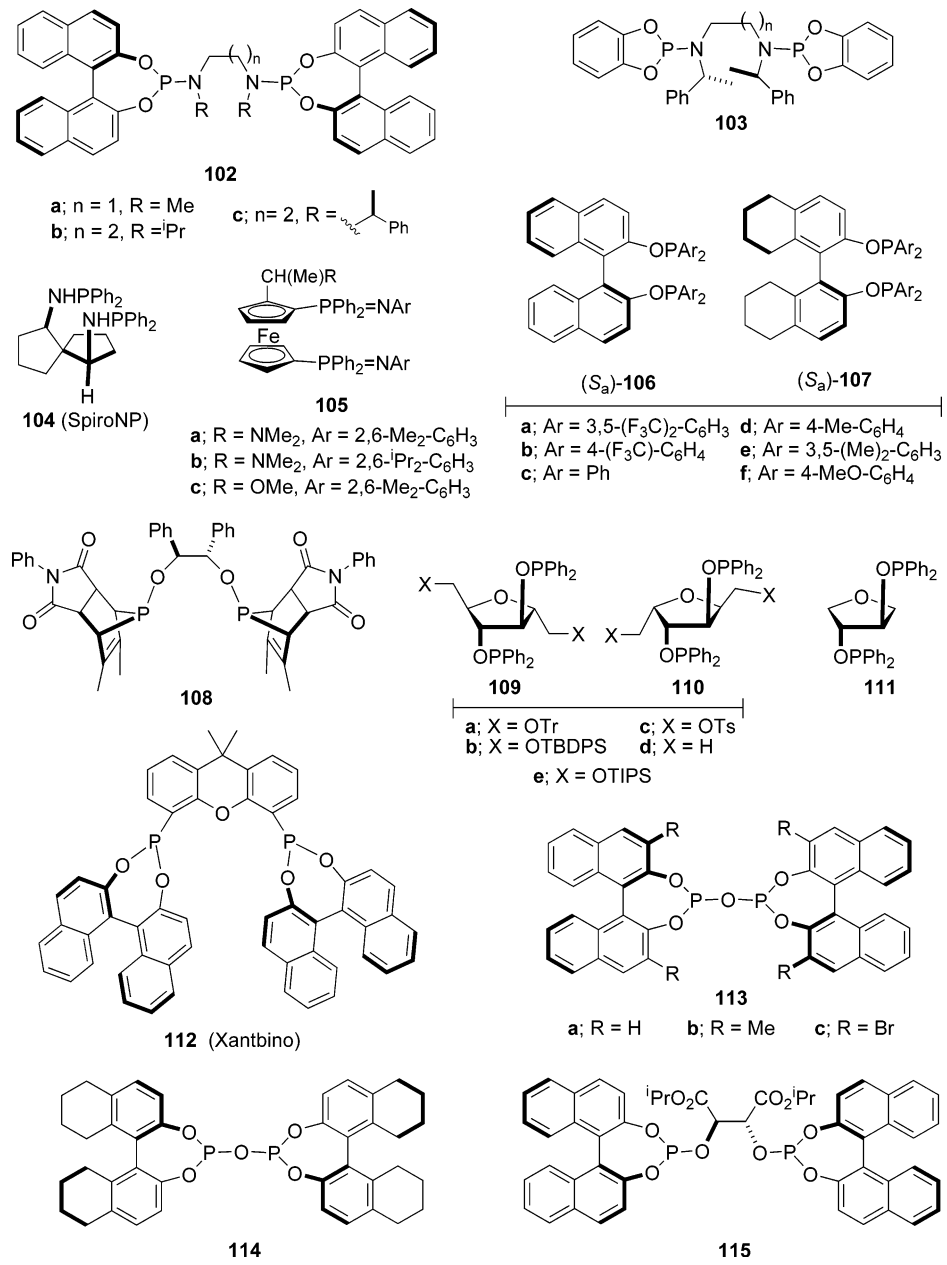
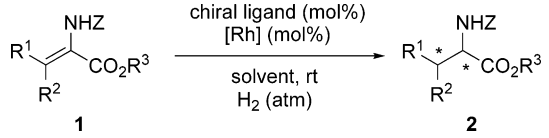


Figure 15. Homobidentate ligands different from bisphosphines.

ready to promote the title reaction onto molecule **1c** in good ee (Table 12, entry 1).[150] Sensibly higher enantioselectivities were offered by the Ru complexes derived from bipyridine ligand **82b** with both methyl ester **1c** and the carboxylic acid **1d**[101] under atmospheric pressure (Table 12, entries 2 and 3). The bisphosphine (S_a)-Binap **87a**−[Ru] complex was employed under different reaction conditions, providing an excellent enantioselectivity (96% ee) for the reaction run in acetone and under 10 atm of hydrogen pressure (Table 12, entry 4).[151,152] The *N*-protected 2-aminopropionic acid, bearing a 4-thiazolyl unit, has been obtained in 77% ee by the intermediacy of a [Ru]−(R_a)-**144** complex (Table 2, entry 5). This α-AA derivative is a very important structural constituent of a renin inhibitor.[153] The three ligands (S_a)-**83**, **97a**, and **145** (Me-f-Ketalphos) were studied in the Ru-catalyzed hydrogenation, under 60 atm of hydrogen pressure, of α-*N*-protected alkenoic acids toward the synthesis of an anthrax lethal factor inhibitor (Table 12, entries 6 and 7).[154] [Ru]−(S_a)-**83** (Figure 13) and [Ru]−**97a** were the most efficient complexes, even in the hydrogenation of isoleucine substrates, giving very high both ee (up to 98%) and de (up to 99%) values.[154] Perfluoroalkylated Binap derivatives (R_a)-**146** and (R_a)-**147** have been employed in the Ru-catalyzed hydrogenation of DAA derivatives **1** in supercritical carbon dioxide with modest ee (Table 12, entry 8).[155] Ir complexes generated from ligands **137**, **148**, (R_a)-**149**, and **150** afforded very different results in terms of the enantioselectivity of the hydrogenation reaction of **1**. Thus, while Ir complexes with **150b** (Table 12, entry 11)[159] and (R_a)-**149**[158] gave modest and very poor results, respectively, the complexes of **137** and **148a**,**b** yielded excellent enantiomeric ratios of the products **2c** under atmospheric pressure (Table 12, entries 9 and 10).[156,157] Finally, the (*R*,*R*)-**59** (Diop)−cobalt complex (Figure 8) was not a useful complex for this reaction, giving compounds **2** with low ee (up to 42%) and employing a very high pressure of hydrogen (50 atm), such as occurred with the combination of this metal with some monodentate ligands previously revised.[44]

Table 10. Enantioselective Synthesis of Compounds 2 Using Homobidentate Ligands 102−115 Complexed with [Rh]



1 2

			1 (Z = Ac)					product 2			
entry	ligand (mol %)	[Rh][a] (mol %)	R^1	R^2	R^3	solvent[b]	P_{H_2} (atm)	conv (%)	config	ee (%)	ref
1	**102c** (1.1)	1	Ph	H	Me	DCM	1	100	(*R*)	80	26
2	**104** (0.2)	0.2	H	H	Me	Me_2CO	1	100	(*R*)	95	121
3	**104** (0.2)	0.2	Ar	H	Me	Me_2CO	1	100	(*R*)	96 to >99	121
4	**104** (0.2)	0.2	H	H	H	EtOH	1	100	(*R*)	78	121
5	**104** (0.2)	0.2	Ar	H	H	EtOH	1	100	(*R*)	84 to >98	121
6	**105a**−**c** (2.1)	2[c]	H	H	Me	MeOH[d]	1	100	(*S*)	83−95	122
7	**105a**,**c** (2.1)	2[c]	Ph	H	Me	MeOH[d]	1	100	(*S*)	93−99	122
8	(S_a)-**107e**,**c** (0.2)	0.5	Ph	H	Me	DCM	7	100	(*S*)	95−99	123
9	**108** (1)	1[e]	Ph	H	Me	MeOH	3	100	(*S*)	94	124
10	**109e** (1)	1	H	H	Me	Me_2CO[f]	1	100	(*R*)	93	125
11	**109e** (1)	1	Ph	H	Me	Me_2CO	1	100	(*R*)	86	125
12	**115** (1)	1	Ph	H	Me	MeOH	1	100	(*R*)	91	129

[a] [Rh] = $[Rh(cod)_2]BF_4$. [b] Reactions run at 25 °C. [c] [Rh] = $[Rh(nbd)_2]BF_4$. [d] Reaction run at 40 °C. [e] [Rh] = $[Rh(cod)_2]PF_6$. [f] Reaction run at −25 °C.

2.2. Reduction of C═N Bonds onto α-Imino Esters

The asymmetric reduction of a C═N double bond, also called indirect reductive amination, forming enantiomerically enriched amines, is one of the most fundamental molecular transformations. In particular, α-imino esters are suitable substrates for the synthesis of α-AA derivatives (Scheme 1, eq b). While simple aliphatic and aromatic aldimines can be efficiently hydrogenated enantioselectively without apparent problems, highly enantioselective hydrogenation of acyclic α-imino esters is considered a difficult task to achieve,[160] and unfortunately, this reason caused this reaction to remain primitive if we compare the numerous examples of the enantioselective hydrogenations or reductions of C═C and C═O bonds. Previously, and during recent years, a few examples of these C═N hydrogenations of α-imino ester derivatives **151** have been published using chiral transition metal complexes of Rh, Ir, and Ru with chiral diphosphines, giving very good ee's (up to >99%), and with chiral zirconocenes, giving good enantioselectivities (76−98% ee).[4b,160]

Recently, highly enantioenriched β-fluorinated α-amino esters **2** (up to 91% ee) were obtained from imino ester **151** (R^1 = BrF_2C, R^2 = PMP, R^3 = Et), under 100 atm of hydrogen pressure, in an asymmetric process promoted by substoichiometric amounts of Pd(II) trifluoroacetate and (*R*)-**87a** (Binap, Figure 13) in fluorinated alcohols, such as 2,2,2-trifluoroethanol, as solvents (Scheme 4).[161] Particularly, the α-AA derivative **2t** and whatever α-AA or peptide possessing two fluorine atoms at the β-carbon can act as potent inactivators of pyridoxal phosphate-dependent enzymes, blocking important metabolic pathways.[162] In the search for new molecules incorporating this atomic array, compound **2t** was conveniently transformed (employing a radical allylation followed by oxidative cleavage of the newly generated carbon−carbon double bond) into optically active β,β-difluoroglutamic acid and β,β-difluoroproline derivatives.[162]

N-Aroylhydrazones **152** underwent a Rh-catalyzed enantioselective hydrogenation reaction in quantitative yield under very mild reaction conditions. The highest ee's, obtained for hydrazines **153**, were achieved with the (*R*,*R*)-Et-Duphos **67b**−[Rh] complex (Figure 12) as catalyst in the reaction with the methyl ester derivative (R^2 = Me) (Scheme 5).[163] However, these hydrazines **153** have not been further transformed into the corresponding α-AAs.

Ketone oximes **154**[164] and nitrones **155**[165] bearing an ester group (Figure 18) were used as substrates in the catalytic enantioselective hydrogenation reaction mediated by Ir and Ru complexes, respectively. In both cases, the highest enantioselectivities (91−93%) were obtained in processes occurring with very low conversions (up to 24%) in spite of the numerous reaction conditions tested.

The asymmetric catalytic reduction of simple aromatic and aliphatic aldimines and ketimines with certain organohydrosilanes and transition-metal catalysts represents a versatile method for the obtainment of primary and secondary alkylamines.[4b,160,166] This metal-catalyzed enantioselective hydrosilylation reaction has emerged as an alternative route to the classical hydrogenation, avoiding the high pressures of hydrogen, and at this moment, it can achieve a sufficient level to be a preparative method for the asymmetric reduction of C═N double bonds. Chiral bisphosphine− or aminophosphine−Rh and −Ti catalytic complexes are, in this order, the most frequent complexes successfully employed in the reduction of imines, although some isolated examples with other transition metals are reported in the literature.[4b,160,166] For the synthesis of α-AA derivatives, the appropriate substrates required are *N*-protected α-imino esters, which have been prepared previous to the reduction step.

Recently, it has been found that *N*-phosphinyl imino esters **156** underwent chemo- and enantioselective hydrosilylation reactions through a rare example of catalysis by the Re-(V)-oxo complex **157**, unveiling its potential for use in nonoxidative enantioselective transformations. This cyanobis(oxazoline) chiral ligand, which has been found to be an efficient ligand for cations of copper, zinc, titanium, etc., formed a bright green solid with a sophisticated Re(V) salt, where the metal atom possessed a distorted octahedral geometry. The hydride source ($PhMe_2SiH$) used in excess (2 equiv) furnished *N*-phosphinyl arylglycines **2u** with excellent ee and modest to good chemical yields (Scheme 6).[167]

A metal-free organocatalytic hydrosilylation protocol, which is competitive with the metal-catalyzed methodology,

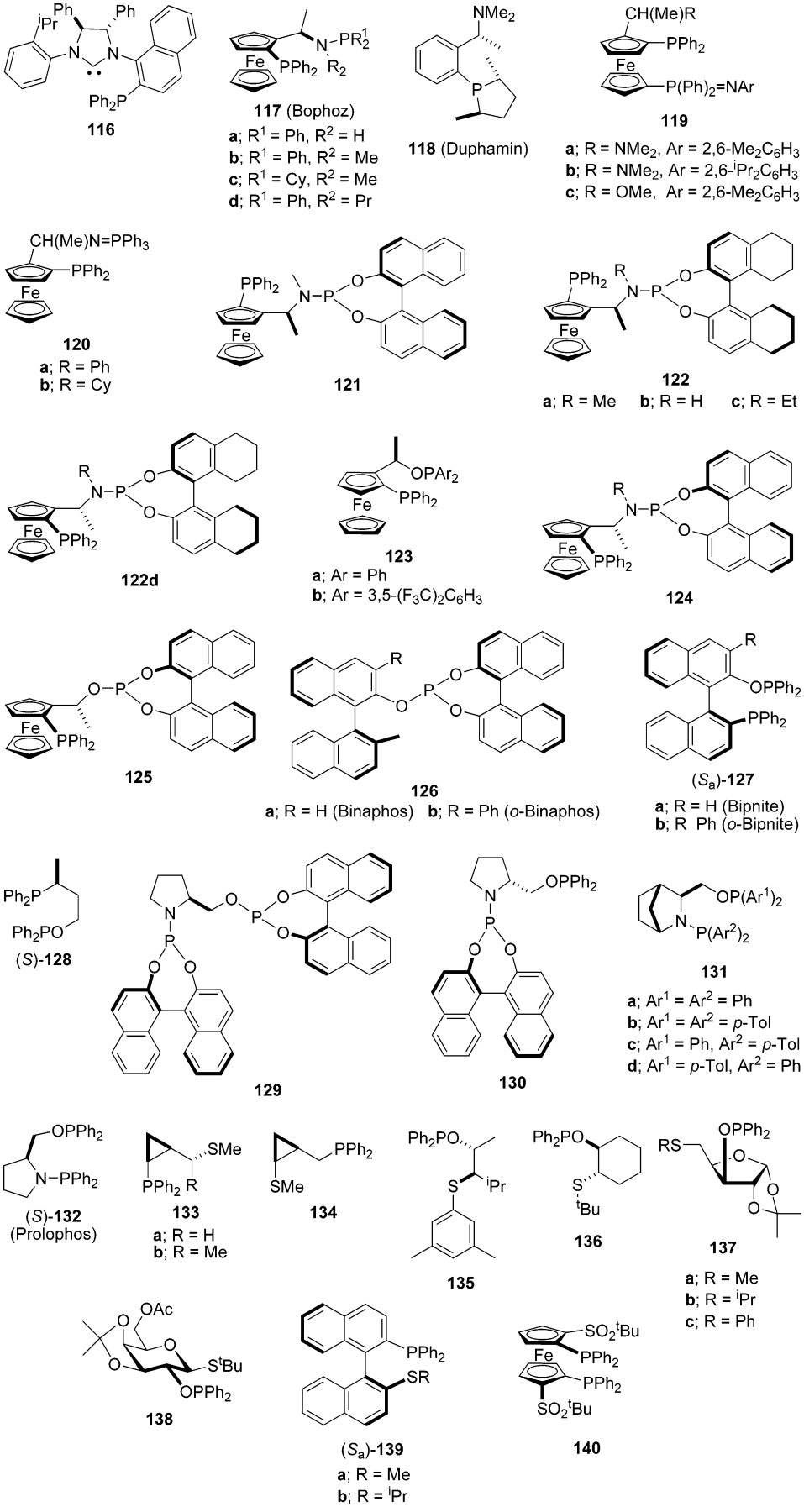
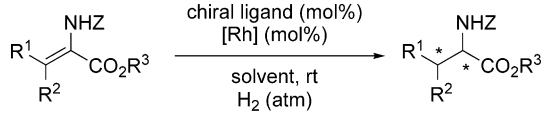


Figure 16. Heterobidentate ligands **116**−**140**.

Table 11. Enantioselective Synthesis of Compounds 2 Using Heterobidentate Ligands 116−140 Complexed with [Rh]



1 **2**

			1 (Z = Ac)					product **2**			
entry	ligand (mol %)	[Rh][a] (mol %)	R^1	R^2	R^3	solvent[b]	P_{H_2} (atm)	conv (%)	config	ee (%)	ref
1	**116** (1.1)	1	H	H	Me	DCE[c,d]	20	100	(*S*)	99	130
2	**116** (1.1)	1	Ph	H	Me	DCE[c]	30	98	(*S*)	98	130
3	**117b** (1)	1	Ar	H	Me	THF	0.7	>99	(*S*)	98 to >99	132, 134
4	**117b** (1)	1	Ph	H	H	THF	0.7	>99	(*S*)	>99	132
5	**117b** (1)	1	H	H	Me	THF	0.7	>99	(*S*)	99	132
6	**117b** (1)	1	C_3H_5	H	Bn[e]	EtOAc	0.7	100	(*S*)	>99	131
7	**119a−c** (2.1)	2[f]	H	H	Me	MeOH[g]	1	100	(*S*)	92 to >99	122
8	**119a−c** (2.1)	2[f]	Ph	H	Me	MeOH[g]	1	100	(*S*)	99	122
9	**121** (0.2)	0.1[h]	Ph	H	Me	DCM	10	100	(*R*)	>99	136
10	**122a−c** (1.1)	1[h]	Ar	H	Me	DCM	10	100	(*R*)	>99	137
11	**123b** (1)	1[h]	Ar	H	Me	DCM/MePh	10	100	(*S*)	97 to >99	138
12	**124** (1)	1[h]	Ar	H	Me	THF	20	100	(*S*)	97 to >99	138
13	**126b** (1.1)	1[i]	H	H	Me	THF	1	100	(*S*)	>99	139
14	**127b** (1.1)	1[i]	H	H	Me	THF	1	100	(*S*)	>99	139
15	**126b**[j] (1.1)	1[i]	Ar	H	Me	THF	1	100	(*S*)	>99	139
16	**131a** (1)	1[h]	Ph	H	Me	MeOH	1	100	(*S*)	91	142
17	**135** (1)	1[k]	Ar	H	Me	THF	1	100	(*S*)	92−97	144
18	**136** (1)	1[k]	Ar	H	Me	THF	1	100	(*S*)	94−98	144
19	**137b** (1.1)	1[h]	H	H	Me	DCM	30	83	(*R*)	96	145
20	**137b** (1.1)	1[h]	Ph	H	Me	DCM	30	100	(*R*)	93	145
21	**138** (1.1)	1[k]	Ph	H	Me	DCM	4	100	(*S*)	92	146
22	**140** (0.5)	0.5[k]	H	H	Me	MeOH	3	>99	(*S*)	93	148

[a] [Rh] = [Rh(cod)$_2$]OTf. [b] Reactions run at 25 °C. [c] DCE = 1,2-dichloroethane. [d] Reaction run at 70 °C. [e] *N*-Boc DAA derivative was employed. [f] [Rh] = [Rh(nbd)$_2$]BF$_4$. [g] Reaction run at 40 °C. [h] [Rh] = [Rh(cod)$_2$]BF$_4$. [i] [Rh] = [Rh(cod)$_2$]PF$_6$. [j] Or compound **127b**. [k] [Rh] = [Rh(cod)$_2$]SbF$_6$.

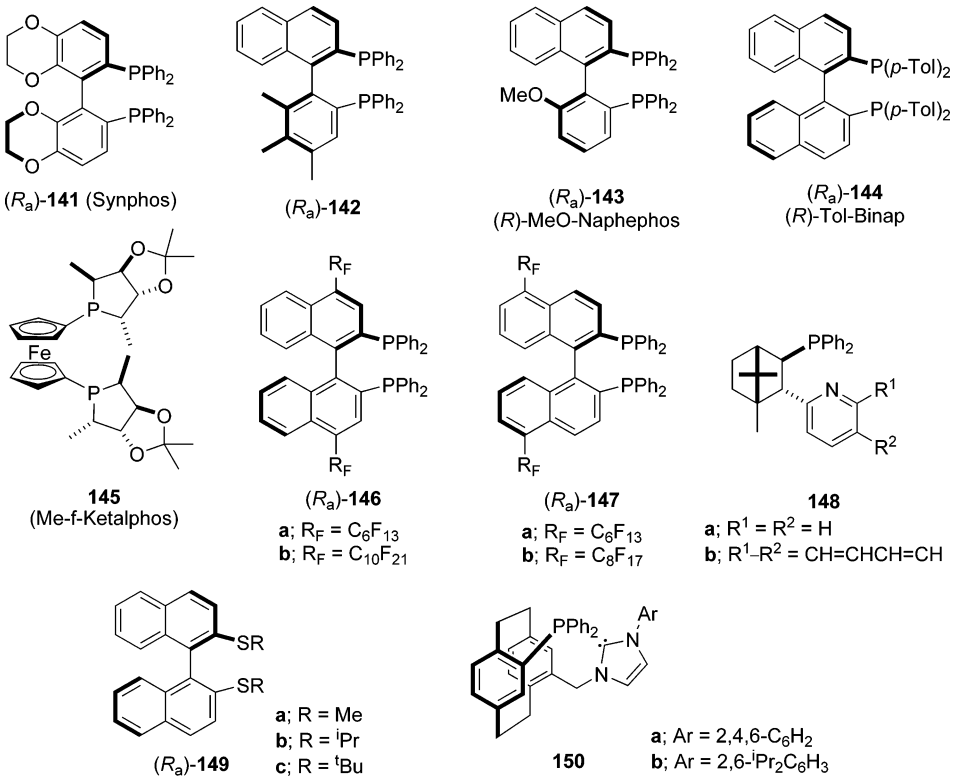
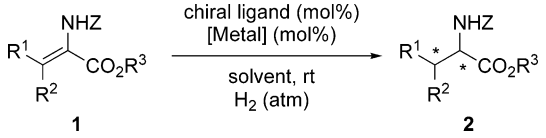


Figure 17. Bidentate ligands for other metals different from Rh.

has been recently applied to the synthesis of α-AA derivatives. The unique example described to date concerns a formamide derived from valine **159** (10 mol %), which was employed as organocatalyst in the hydrosilylation of α-imino ester **158** (R^1 = R^2 = Ph, R^3 = Me) with trichlorosilane at −20 °C, affording the phenylglycine derivative **2v** with ee of 69% in 70% yield (Scheme 7).[168,169] The proposed transition state involved, possibly, a potent amide−imine hydrogen bonding and a π-stacking interaction as key elements for the enantiodiscrimination.[168]

Table 12. Bidentate Ligands 141−150 in the Enantioselective Hydrogenation of Alkenes 1 Catalyzed by Metals Different from Rh

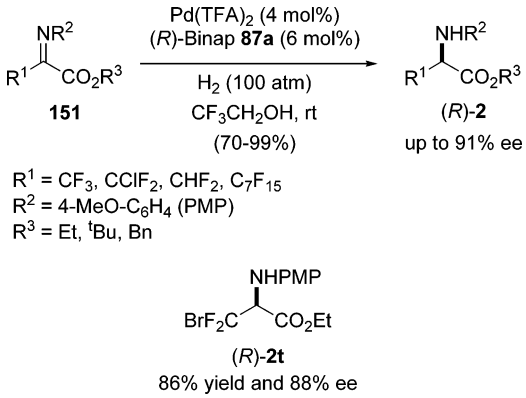


1 2

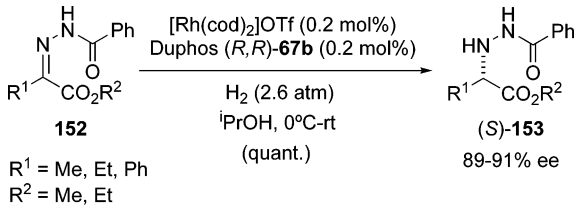
			1 (Z = Ac)					product 2			
entry	ligand (mol %)	metal salt (mol %)	R^1	R^2	R^3	solvent	P_{H_2} (atm)	conv (%)	config	ee (%)	ref
1	**141** (1.1)	[Ru(cod)(2-methylallyl)$_2$] (2)	Ph	H	Me	MeOH[a]	5	100	(*S*)	86	150
2	(S_a)-**82b** (1)	[Ru(Cl)(C_6H_6)]$_2$ (1)	Ph	H	Me	MeOH[a]	1	>99	(*R*)	99	101
3	(S_a)-**82b** (1)	[Ru(Cl)(C_6H_6)]$_2$ (1)	Ph	H	H	MeOH[a]	1	>99	(*R*)	90	101
4	(S_a)-**87a** (2)	[Ru(cod)(2-methylallyl)$_2$] (2)	Ph	H	Me	Me_2CO[a]	10	>99	(*R*)	96	152
5	(R_a)-**144** (1)	$RuCl_3$ (1)	Het[c]	H	Me	MeOH[a]	50	>99	(*S*)	77	153
6	**97a** (1)	[(*p*-cymene)$RuCl_2$]$_2$ (1)	Me	Me	H[d]	EtOH[a]	6	>99	(*R*)	98	154
7	(S_a)-**83** (1)	[(*p*-cymene)$RuCl_2$]$_2$ (1)	Me	Me	H[e]	EtOH[a]	6	95	(*R*)	99	154
8	(R_a)-**146a** (0.2)	[Ru(Cl)(C_6H_6)]$_2$ (0.2)	Me	H	H	sCO_2/CF_3Ph[b]	20	100	(*R*)	74	155
9	**148a**,**b** (1)	[Ir(cod)Cl]$_2$ (1)	Ph	H	H	DCM/MeOH[b]	1	100	(*S*)	97	156
10	**137a** (1)	[Ir(cod)Cl]$_2$ (1)	Ph	H	Me	DCM/MeOH[b]	1	100	(*S*)	97	157
11	**150b** (1)	[Ir(cod)Cl]$_2$ (1)[f]	Ph	H	Me	DCM/MeOH[a]	50	100	(*S*)	71	159

[a] Reactions run at 25 °C. [b] Reactions run at 50 °C. [c] Het = 4-thyazolyl. [d] *N*-*p*-Toluenesulfonamido DAA derivative **1**. [e] *N*-Cbz DAA derivative **1**. [f] NaBARF was added (BARF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate).

Scheme 4



Scheme 5



The asymmetric transfer hydrogenation is another operationally simple process employing stoichiometric chiral hydrogenation agents, but unfortunately, a low number of successful examples have been reported for simple imines.[160,170] Even more scarce are the examples of this hydride transfer reaction onto α-imino esters **158**. To the best of our knowledge, the unique example reported in the literature where an α-AA derivative was synthesized was inspired in the biosynthetic NADH model using magnesium salts where a stochiometric chiral dihydropyridine was employed as hydride source.[171]

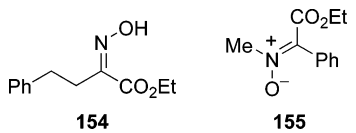
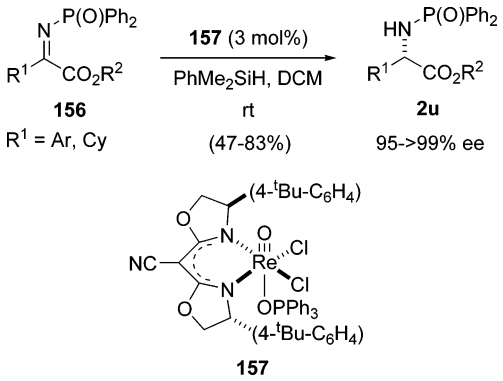
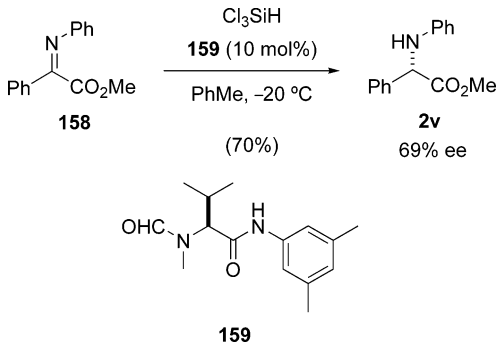


Figure 18. Molecules **154** and **155**.

Scheme 6



Scheme 7



2.3. Reductive Amination of α-Keto Acids and α-Keto Esters

The direct reductive amination (or single-stage amination) represents the classical reductive amination concept where a mixture of the carbonyl compound and the amine is directly treated in the presence of a reducing agent.[172] The preceding section described the indirect reductive amination involving the reduction of the already prepared α-imino esters from the corresponding α-keto ester. The first example of an enantioselective version in 1999 was dedicated to the synthesis of the herbicide (*S*)-metolachlor, employing an Ir complex with a chiral diphosphine onto an aryl imine.[172] The examples described with alkyl- and arylamines are not

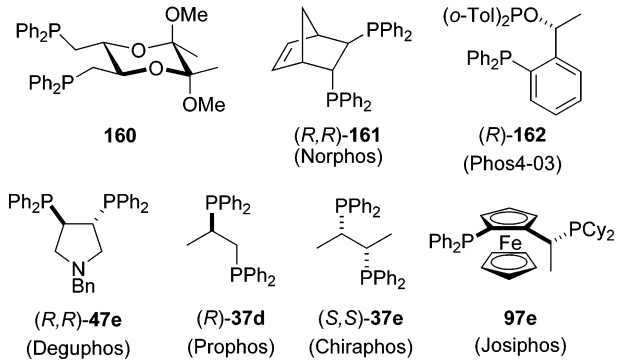
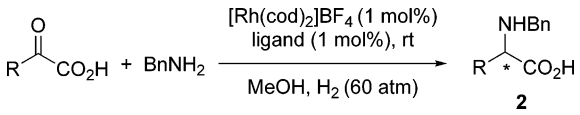


Figure 19. Some chiral ligands essayed in the enantioselective reductive amination of α-keto acids **159**.

Table 13. Rh-Catalyzed Enantioselective Reductive Amination of α-Keto Acids 159



			products **2**			
entry	R	ligand	conv (%)	config	ee (%)	ref
1	$PhCH_2$	(*R*,*R*)-**160**	60	(*R*)	38	173a
2	$PhCH_2$	(*R*,*R*)-**47e**	>99	(*S*)	97	173b
3	Me	(*R*,*R*)-**47e**	43	(*S*)	78	173b
4	HO_2CCH_2	(*R*,*R*)-**47e**	38	(*S*)	73	173b
5	$PhCH_2CH_2$	(*R*,*R*)-**47e**	79	nd	81	173b
6	$^{i}PrCH_2$	(*R*,*R*)-**47e**	99	(*S*)	90	173b
7	$^{i}PrCH_2$	(*R*,*R*)-**161**	46	(*S*)	61	173b
8	$^{t}BuCH_2$	(*R*,*R*)-**47e**	94	nd	86	173b
9	$^{t}BuCH_2$	(*R*,*R*)-**161**	32	nd	60	173b

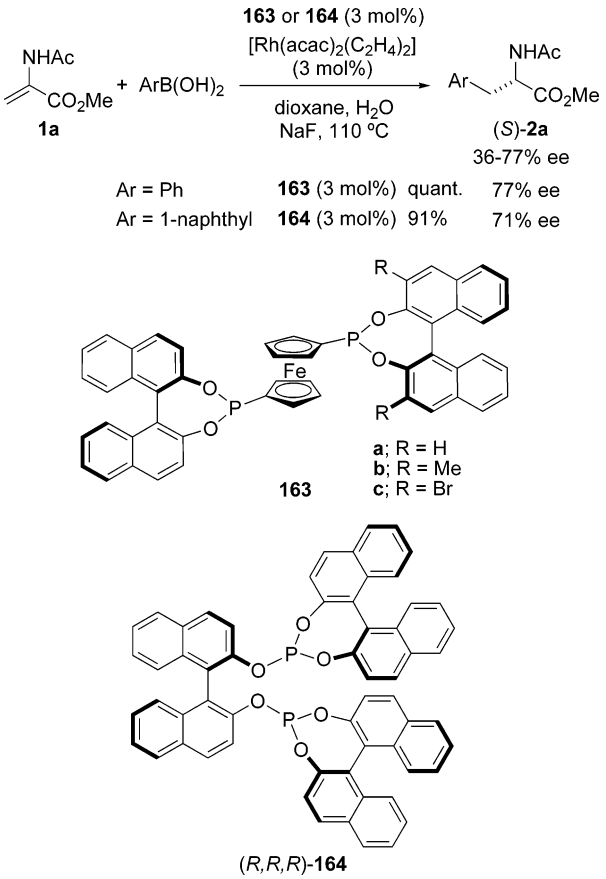
numerous, and even less abundant are the reactions of α-keto acids or esters under this direct reductive amination.

α-Keto acids and benzylamine were put together in the Rh-catalyzed hydrogenation reaction using different diphosphines as ligands (Figure 19), under mild reaction conditions, obtaining products **2** with enantioselectivities ranging from 38 to 97% ee (Table 13). In the first catalytic enantioselective reductive amination, it was clearly demonstrated that the most efficient catalytic complex was (*R*,*R*)-**47e**−[Rh].[173] The best enantioselection was obtained when phenylpyruvic acid and α-isopropylpyruvic acid were used as starting materials (Table 13, entries 2 and 6). On the other hand, the ligand (*R*,*R*)-**160**−[Rh] complex[173a] (Table 13, entry 1) and the ligand (*R*,*R*)-**161**[173b] (Table 13, entries 7 and 9) did not generate such efficient enantioselectivities for this particular transformation. With ligands **37d**, **37e**, **97e**, and **162** (Figure 19), the reaction did not occur at all or with very low enantioselections.[172]

2.4. Protonation of Enolates

The enantioselective protonation of enolates with a chiral protonating source provides a very easy way to create a stereogenic center by the formation of a C−H bond (Scheme 1, eq c). Initially, an excess of equimolar amounts of an enantioselective protonating agent was required, and the employment of substoichiometric quantities was not very successful. As also occurred in the enantioselective reduction of imines, this transformation involving chiral protonating sources is too complex, and it has been continuously improved since 1977.[174] Multiple factors govern the enantioselectivity of the final product, for example, the structure

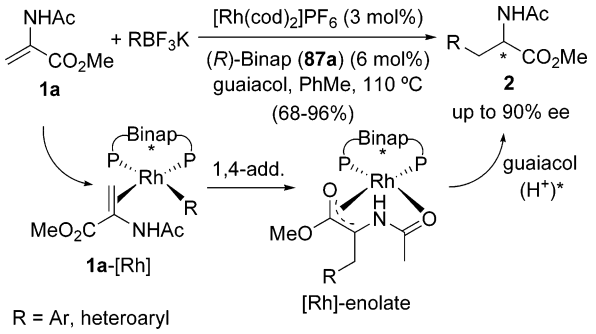
Scheme 8



of the protonating agent, its acidity requirements versus the acidity of the enolate, the structure of the substrates, and the reaction medium, and it is important to take into account the (*E*/*Z*)-ratio of the enolate (latent-trigonal center concept). Moreover, the availability, cost, and easy recovery of the chiral protonating agent after use must obviously be taken into consideration as well.[174] Usually, stoichiometric amounts of the chiral protonating agents have been employed onto imino esters derived from glycine, alanine, phenylalanine, valine, leucine, phenylglycine, and prolines for the synthesis of α-AAs.[174b−d] However, a catalytic enantioselective protonation can be achieved from a Michael-type addition reaction, which generates an intermediate enolate. This enolate can be coordinated with a chiral ligand or even with a chiral−metal complex to form a chiral complex or a chiral aggregate, which were brought into the presence of an achiral acid. The Rh- or Cu-catalyzed asymmetric Michael-type additions are followed by the reaction of this transient enolate with electrophiles, but the use of the protonation as an electrophilic pathway after the 1,4-addition onto DAA derivatives was not reported until 2001.[175]

Bisphosphinite **163** and bisphosphite **164**, used in substoichiometric amounts, were employed as complexating agents of the enolates generated by the Rh-catalyzed 1,4-Michael-type addition reactions of areneboronic acids onto α-acetamidoacrylate **1a**. First, the enantioselective protonation occurred by the *Si*-face of the carbon−carbon double bond of **1a**, when ferrocene **163** was employed in refluxing water/1,4-dioxane in the presence of sodium fluoride as base.[175] In this example, the interval of ee obtained for compounds (*S*)-**2** was very similar (36−77% ee) to the range of ee obtained later when employing ligand **164** (Scheme 8). This bisphosphite **164** assisted the enantioselective

Scheme 9



protonation of the corresponding enolate in good yields and ee's ranging from 36 to 72% under exactly identical reaction conditions to those described when ligand **163** was employed (Scheme 8).[176]

The chiral (*R*)-Binap **87a**−[Rh] complex (Figure 13) first interacts with the DAA derivative **1a**, generating a new complex **1a**−[Rh], which gave the corresponding Rh−enolate complex after the 1,4-conjugate addition reaction of the potassium alkyltetrafluoroborate. At the end of the process, the title catalytic enantioselective protonation was mediated by guaiacol (an achiral protonation agent), which was able to protonate the chiral [Rh]-enolate. The highest ee's were obtained when R was a phenyl substituent, although other aromatic, heteroaromatic, and vinyl substituents could be successfully bonded in very good yields and high enantioselections ranging from 81 to 90% ee (Scheme 9).[177]

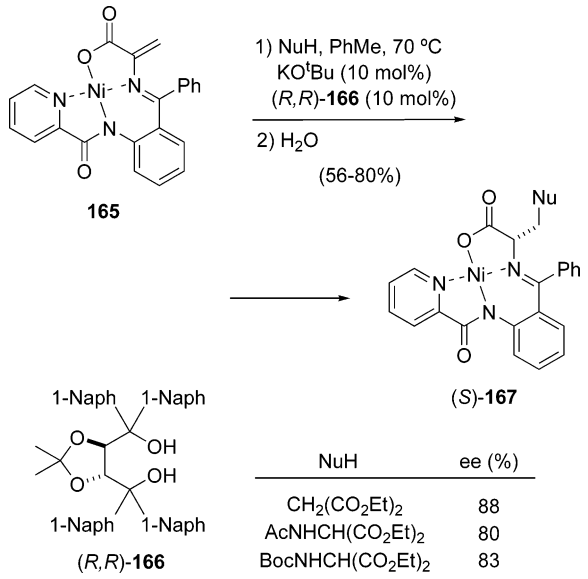
The Michael-type addition reaction of stabilized enolates onto the DAA derived from iminic nickel carboxylate **165** proceeded at 70 °C, in the presence of 10 mol % of (*R,R*)-taddol derivative **166** as chiral ligand, with the protonation agent being *tert*-butyl alcohol, which was originated as a byproduct of this reaction. The function of **166** might be to increment the malonic ester acidity by hydrogen bonding and forming a chiral environment for recognition of the enantiotopic enolate. The products **167** were isolated in good yields and high ee's (up to 88%), with better results being obtained when diethyl malonate was employed as the carbonucleophile, while the analogous diethyl α-amidomalonates gave sensibly lower enantioselectivities (Scheme 10).[176,178]

2.5. DKR−Metal-Catalyzed Hydrogenation

Another type of reaction able to introduce enantioselectively the α-hydrogen is depicted in Scheme 1 (eq d). For using this strategy in this context, α-amino *β*-keto esters are mainly the selected starting materials, although it would also be also possible working with other carboxylic acid derivatives as precursors, containing a nitrogenated group at the α-position and an oxo-functionality at the *β*-position. Presumably, a dynamic kinetic resolution occurred through the formation of the chiral metal complex-1,3-dicarbonyl compound, previously to the carbon−oxygen double bond, due to the high acidity of the α-hydrogen of these 1,3-dicarbonyl compounds.

Since the seminal work of Noyori's group, using the (*R*)-Binap **87a**−[Ru] complex in the study of the high enantioselection observed in the enantiodiscrimination, occurred in labeled 1,3-dicarbonyl compounds,[179] the dynamic kinetic resolution (DKR), in association with the Ru-, Rh-, or Ir-catalyzed hydrogenation, turned out to be a powerful

Scheme 10

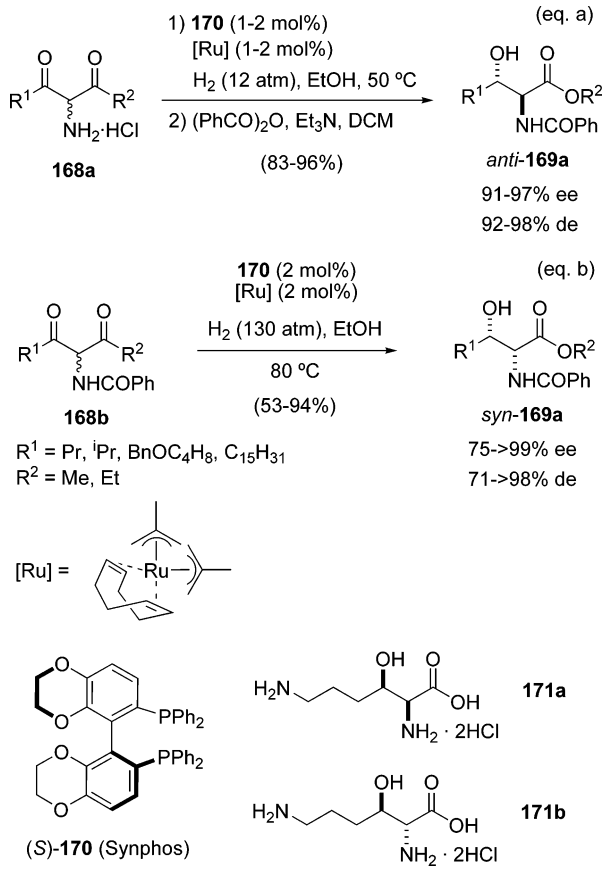


synthetic tool to control two adjacent stereogenic centers, as occurred in racemic α-amino *β*-keto ester derivatives **168**, in one single chemical operation.[10n,179] Three research groups independently published their results of the hydrogenation onto racemic compounds **168**, introducing very interesting synthetic alternatives.[180−185] For example, the (*S*)-Synphos **170**−[Ru] complex was a very efficient catalysts, rather than the (*R*)-MeO-Biphep **77b**−[Ru] complex (Figure 13), for the asymmetric hydrogenation of the α-amino *β*-keto esters **168a** and **b**, giving enantiomerically enriched α-amino *β*-hydroxy esters *anti*-**169** in very good yield and excellent ee and de (Scheme 11, eq a). Similarly, the α-amino *β*-keto esters **168b** reacted under mild reaction conditions to afford compounds *anti*-**169**, after benzoylation of the corresponding amino group, in excellent yield and both ee and de (Scheme 11, eq b). The advantage of using these pure hydrochlorides was the relative low pressure of hydrogen needed for achieving almost total conversions. This elegant methodology can be considered as a valuable alterative to the hydrogenation and to the electrophilic amination (see next section) for the synthesis of both *anti*- and *syn*-stereoisomers of α-amino *β*-hydroxy acids from the same common readily available keto esters **168**, only by modification of the substituents bonded to the amino group.[180,181] One of the multiple applications of this methodology was exemplified in the leading work dealing with the synthesis of the α-AAs **171a** and **b**, which were finally obtained by acidic hydrolysis of a terminal phthalimido group and the acetamido group placed at the α-position.[182] Particularly, **171a** has been employed for the construction of the functionalized azepane core present in the protein kinase C (PKC) inhibitor (−)-balanol.[182]

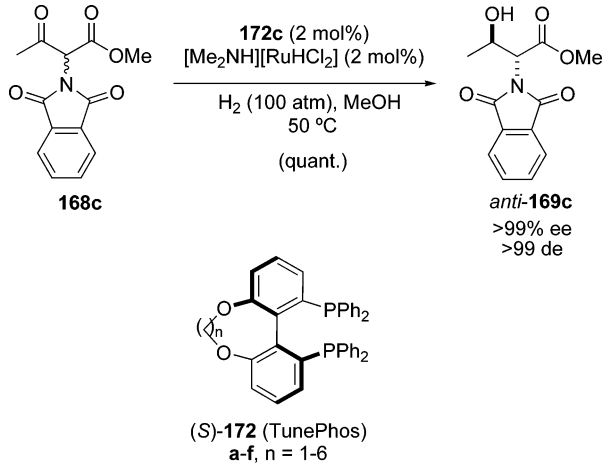
Also, high *anti*-selectivity was exhibited by the (*S*)-TunePhos **172c**−[Ru] complex in the hydrogenation−DKR of the racemic 2-phthalimido-1,3-dicarbonyl compound **168c** (>99 ee and *anti*/*syn* ratio >97:3) in very good chemical yield. Once more, the pressure of hydrogen required for the completion of the successful transformation was quite high (Scheme 12).[183]

The Ir complex formed by the coordination with (*S*)-Binap **87a** gave very high diastereomeric ratios and lower ee than when the ligand Synphos **170** was used. Nevertheless, the (*S*)-MeO-Biphep **77b**−[Ir] complex induced excellent de (>99%), and the ee was higher than the ee reported for these

Scheme 11



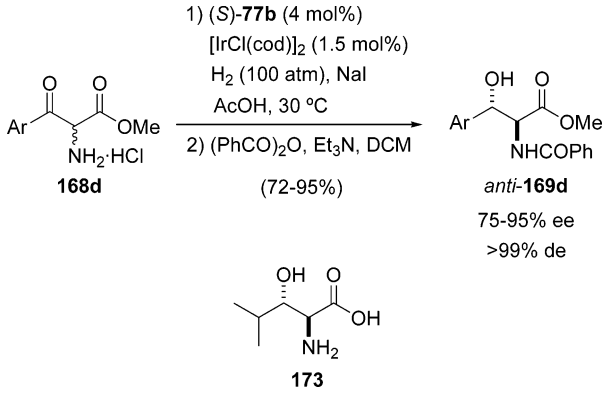
Scheme 12



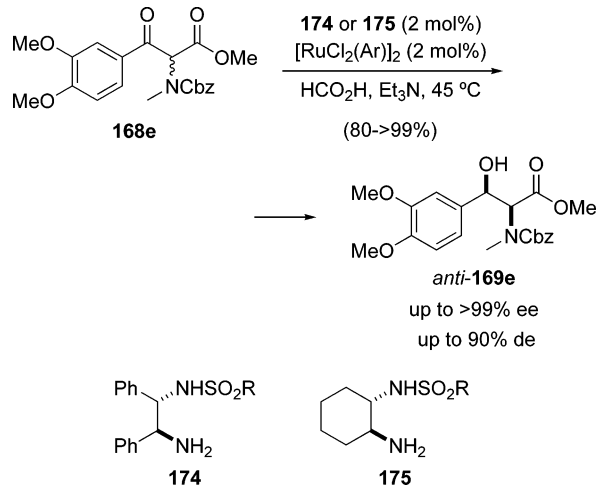
two previous Ir complexes. Despite using the amine hydrochloride **168d**, the required operational pressure of hydrogen to obtain **169d** was 100 atm (Scheme 13).[184] 3-Hydroxyleucine **173** and its enantiomer can be prepared through this synthetic pathway after the corresponding acidic hydrolysis. Naturally occurring hydroxyleucines have been found in the ester tether linkage in natural cyclodepsipeptides, such as papuamides and polyoxypeptides.[185]

It was unveiled that chiral *β*-amido amines **174** and **175** were effective ligands in the Ru-catalyzed asymmetric transfer hydrogenation−DKR of the racemic Dopa-mimetic **168e** using formic acid, furnishing the final optically active **169e** in high yield and excellent stereoselection (Scheme 14), which is a potential pharmacophore to be applied for multiple purposes.[186] This method is a powerful alternative to asym-

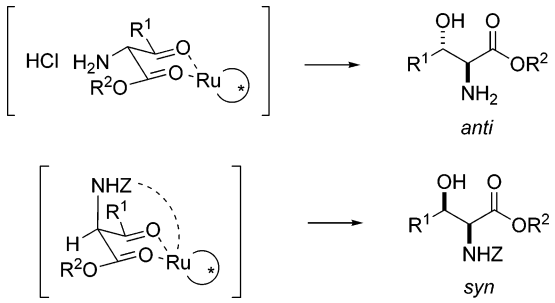
Scheme 13



Scheme 14



Scheme 15



metric hydrogenation due to its practical simplicity and the possibility of using easily accessible and less sensitive ligands. Previous to the hydrogen transfer, the formation of a chiral Ru complex coordinates intramolecularly both carbonyl and Cbz-amino groups. The Cbz-amino group can adopt its optimal configuration by intermediacy of the base in order to construct the active catalytic species.

Although there is not clear evidence to explain the stereochemical outcome of the hydrogenation of substrates **168**, it was postulated that the reaction process occurred through a favored chairlike transition state where the ketone and the ester carbonyls are chelated to the Ru atom and the ammonium group is placed in a pseudoequatorial position. Moreover, an electron-withdrawing group bonded to the nitrogen atom would coordinate efficiently to the metal center to generate the *syn*-diastereoisomer as major product (Scheme 15).[180] These processes can be considered as an example of enantioselective introduction of the H_α atom because the enolizable starting materials can adopt the optimal conforma-

tion in this chairlike model through the intermediate enolate during the DKR stage, allowing a repositioning of this H_α atom.

As a short summary, we can conclude that the catalytic enantioselective hydogenation of DAA derivatives allows the synthesis of α-monosubstituted α-AA, and the most appropriate substrates are 1,1-disubstituted or 1,1,2-trisubstituted alkenes **1**, which are very easily obtained through standard methodologies. The reactions are preferred to occur at lowest hydrogen pressures, employing the minimal amount of chiral metal complex and offering very high enantioselections. All these requirements can be accessed, for example, with Rh complexes formed with ligands (S_a)-**3**, (S_a)-**4** (Table 1), (*S*)-**33**, **41**, **42**, **44** (Table 5), (*R*,*R*)-**69** (Table 7), and **104** (Table 10). However, for tetrasubstituted alkenes **1**, very few catalytic chiral complexes are operative. For instance, Rh complexes formed from ligands (R_a)-**7** (Table 1) and (*S*)-**33** (Table 5) under 1 atm hydrogen pressure and Ru−(S_a)-**83** complex formed under 6 atm hydrogen pressure (Table 12) gave the best enantioselections. A drawback of this strategy is the recuperation and reutilization of the catalysts, so many efforts are currently underway in order to improve the economy, quality, and efficiency of these processes. The relatively novel enantioselective catalytic hydrosilylation of α-imino esters is a valuable alternative avoiding the pressure of hydrogen, but much more work has to be developed. The other methods used for the introduction of the α-hydrogen are very interesting when very specific structures, such as a *β*-hydroxy-α-AA, are desired.

3. Enantioselective Introduction of the α-Amino Group

The enantioselective introduction of the α-amino group is one of the most employed strategies for the preparation of α-AA derivatives,[187] especially the electrophilic aminations. These transformations are the most useful tool involving the carbon−nitrogen bond formations through the reaction of ester derived enolates with sources containing an electrophilic nitrogen atom (Scheme 1, eq g). Alternatively, very reactive carbenes or carbenoids, originated from α-diazoesters, also react with imines to afford aziridinecarboxylic acid derivatives (Scheme 1, eq e). Although in less extension, the *in situ* generated nitrenes, able to react with an ester enolate or with alkenes, imply another possibility to construct a carbon−nitrogen bond (Scheme 1, eq f). Asymmetric aminohydroxylations and diaminations are being currently optimized, and there are a few examples using these of oxidations in the presence of reagents bearing an electrophilic nitrogen atom (Scheme 1, eq h). The applications of eq e−h of Scheme 1 into the stereoselective building of α-AA derivatives will be considered in this section.

3.1. Aziridinations

Optically active aziridines, as well as epoxides, are very useful chiral building blocks for synthesis, and in fact, they rival epoxides in their versatility as electrophilic reagents.[3h,188] Whereas a large number of catalytic asymmetric epoxidation methods have been developed, the catalytic asymmetric aziridination showed a relative lack of processes, because the new methods to access them have proven to be exceedingly difficult.[187] Methods using nitrene or carbene precursors and several Lewis acid catalysts have been successfully optimized for enantioselective versions devoted to the synthesis of aziridines.[187] In this part, all these efforts will be focused on the synthesis of the aziridinecarboxylic acids and their derivatives. These cyclic α-AAs are particularly interesting because they affect the chemical and biological properties in peptides through significant conformational restrictions in the α-AA residues.[3n,p,r,s] They are also useful in the search for a new series of constrained α-AAs or valuable intermediates in the synthesis of natural products; different *β*-functionalized α-AAs can be obtained by the heterocyclic ring opening of the titled aziridinecarboxylic acids.[3h,188]

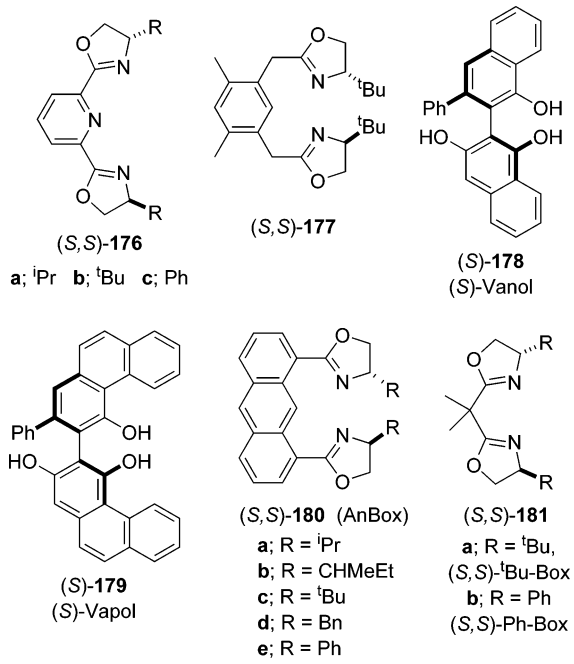
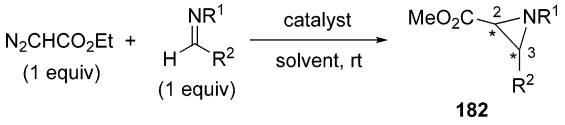


Figure 20. Chiral ligands employed in the enantioselective aziridination.

The asymmetric synthesis of aziridinecarboxylic acids through a catalytic enantioselective aziridination, by reaction of ethyl diazoacetate with aldimines, has been accomplished during these last 2 years[187] using the chiral ligands depicted in Figure 20 to form metallic complexes (Table 14). Pybox−iron complexes derived from ligand (*S*,*S*)-**176** gave very poor enantioselections in very low chemical yield with an elevated diastereoselectivity, with the *cis*-isomer being the major reaction product (Table 14, entry 1).[189] Even more disappointing results were achieved when using the Rh complex formed by bisoxazoline (*S*,*S*)-**177**, which could not afford enantioselections higher than 11% (Table 14, entries 2 and 3).[189] Aziridines **182** were obtained in high chemical yields and excellent enantio- and diastereomeric ratios by employing boron complexes derived from (*S*)-Vanol **178** or (*S*)-Vapol **179** (Figure 20). Both complexes gave very similar results through this process involving the generation and further stabilization of the reactive carbene. The *cis*/*trans* ratio (up to >50/1) was another interesting aspect of this catalytic enantioselective transformation (Table 14, entries 4, 5, and 7).[191,192] The resulting aziridines **182**, obtained by this last approach, were employed for the synthesis of the leukointegrin LFA-1 antagonist BIRT-377 (when Ar = 4-Br−C_6H_4 in **182**), an α-AA derivative (see Scheme 24) developed for the treatment of inflammatory and immune disorders.[192] The synthesis of these enantiomerically enriched aziridines **182** had a crucial contribution in the evaluation of a series of Binol−Banol−Vanol−Vapol ligands in the

Table 14. Enantioselective Synthesis of Aziridines Using Ethyl Diazoacetate

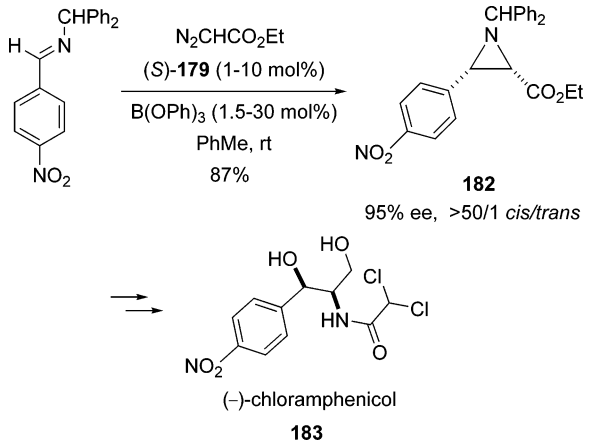


182

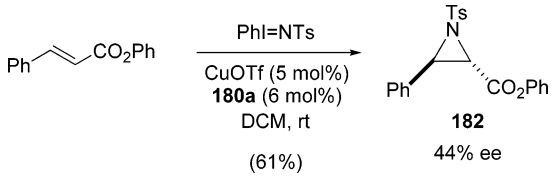
					product **182**				
entry	R^1	R^2	catalyst (mol %)	solvent	conv (%)	cis/trans	config	ee[a] (%)	ref
1	Ph	Ph	(*S*,*S*)-**176b**-$FeCl_2$·$4H_2O$ (5)[b]	DCM	50	>99/1	(2*R*,3*R*)	49	189
2	Ph	4-NO_2-C_6H_4	(*S*,*S*)-**177**-$RhCl_3$·$3H_2O$ (5)	THF	30	>90/10	(2*S*,3*S*)	<12	190
3	Ph	Ph	(*S*,*S*)-**177**-$RhCl_3$·$3H_2O$ (5)	THF	73	75/25	(2*S*,3*S*)	11	190
4	$PhCH_2$	*c*	(*S*)-**178**-$B(OPh)_3$ (0.5−10)	DCM	up to 85	>50/1	(2*R*,3*R*)	up to 96	191, 192
5	$PhCH_2$	*c*	(*S*)-**179**-$B(OPh)_3$ (0.5−10)	DCM	up to 85	>50/1	(2*R*,3*R*)	up to 96	191, 192
6	$PhCH_2$	4-NO_2-C_6H_4	(*S*)-**179**-$B(OPh)_3$ (0.5−10)	PhMe	80	30/1	(2*R*,3*R*)	96	191, 192
7	$PhCH_2$	4-NO_2-C_6H_4	(*S*)-**179**-$B(OPh)_3$ (0.5−10)	PhMe	87	>50/1	(2*R*,3*R*)	87	191, 192

[a] Determined for the major stereoisomer. [b] Ag(I) salts were employed as cocatalysts. [c] Aliphatic and aromatic aldimines were tested.

Scheme 16



Scheme 17

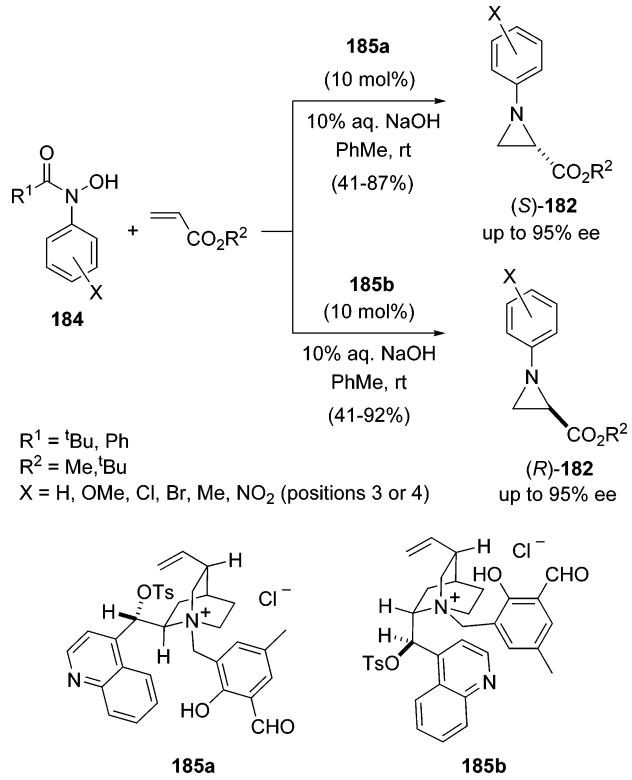


enantioselective aziridination of *N*-benzhydryl aromatic imines. The corresponding aziridine **182** (Ar = 4-$NO_2C_6H_4$) (Table 14, entry 6) was the key step in the efficient synthesis of antibacterial (−)-chloramphenicol **183** (Scheme 16).[193]

A very common source of nitrenes such as [*N*-(*p*-toluenesulfonyl)imino]phenyliodinane (PhI=NTs) reacted with phenyl *E*-cinnamate in the presence of the bisoxazoline (*S*)-**180a** (Figure 20) and CuOTf as catalytic complex to afford the aziridine (2*S*,3*R*)-**182** (R^2 = Ph) in 61% yield and with a 44% ee (Scheme 17).[194] Other AnBox ligands (*S*)-**180** as well as Box ligand (*S*)-**181** were essayed under the same reaction conditions, but no improvement of the ee was achieved.[194]

A second strategy for the aziridination of α,β-unsaturated esters involves the use of chiral phase-transfer catalysts (PTC) derived from *Cinchona* alkaloids. Thus, ammonium salts **185a** and **185b**, in the presence *N*-acyl-*N*-arylhydroxylamines **184**, as generator of nitrene species and electron-deficient alkenes furnished enantioenriched aziridines **182**. The optimum conditions for the reaction were the employment of a low concentration of aqueous NaOH

Scheme 18

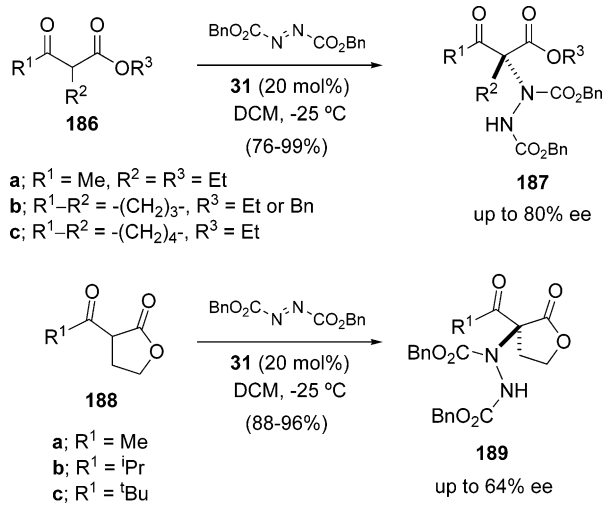


in toluene, in order to promote the α-elimination for generating the nitrene, and 10 mol % loading of the organocatalyst **185a** or **185b** (Scheme 18). The precursor of the nitrene, the alkene, and the chiral PTC agent seem to form a molecular assembly governed by electrostatic interactions, which made possible a very efficient stereoselectivity.[195] Generally, a (*R*)-configuration on the aziridines **182** (R^2 = H) was induced by the cinchonine-derived chiral catalyst **185a**, while the corresponding enantiomer could be obtained by the use of the chiral cinchonidine-derived PTC agent **185b**.[195]

3.2. Electrophilic Aminations

One of the most direct and simple approaches to α-AAs is the amination of enolates with electrophilic reagents; unfortunately, only a few suitable nitrogenated reagents have so far been identified and essayed in diastereoselective processes.[3s−z] One of the first was di-*tert*-butyl azodicarboxylate, followed by a more promising agent, such as trisyl

Scheme 19



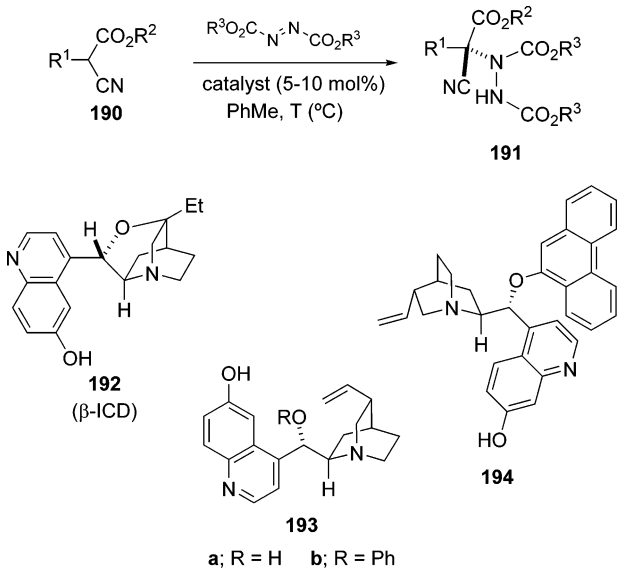
azide.[3w] This "umpolung" methodology for the formation of a carbon−nitrogen bond has been the subject of several revisions, including new nitrogen reagents acting as "NH_2^+" equivalents versus all type of enolates.[196] One of the featured aspects of this methodology involves the further nitrogen−nitrogen bond cleavage using reduction protocols.

Very recent examples of the catalytic enantioselective electrophilic α-amination of enolates appeared during the last 3 years, dealing with chiral organocatalysts or with chiral transition metal complexes. *β*-Keto esters **186** and *β*-keto lactones **188** reacted with dibenzyl azodicarboxylate under the reaction conditions described in Scheme 19.[197] When cinchonine **31** (Figure 6) was used as organocatalyst (20 mol %), at −25 °C in DCM, compounds **187** and **189** were obtained with ee up to 80% and 64%, respectively.[197] The cinchonidine **32** (Figure 6) was also studied as a chiral organocatalyst, affording, in general, lower enantioselections of the corresponding *β*-keto compounds **187** and **189** but with opposite configuration at the stereogenic center. Presumably, these catalysts act as chiral bases, allowing the possibility to form some hydrogen bonding between the hydroxy group and the carbonyl group of the enolizable reagent.

α-Cyanocarboxylates **190** have been selected as substrates in the electrophilic amination reaction using dialkyl azodicarboxylates employing chiral bases as organocatalysts **192**−**194** (Scheme 20 and Table 15). Ligands (*β*-ICD) **192** and **194** afforded excellent enantioselections of the quaternized products (*S*)-**191** at very low temperatures (Table 15, entries 1 and 4−7).[198] In this work, the study of the enantioselection of the ligand *β*-ICD-**192** was performed with 1,3-dicarbonyl compounds **186** and **188**, obtaining analogous results to those previously described for the organocatalytic reaction mediated by cinchonine **31**.

Through a different mechanism, proline, which is certainly part of a set of organocatalytic reagents able to promote a broad range of transformations,[200] proved to be a good organocatalyst for the electrophilic enantioselective amination.[201] Aldehydes are particularly useful substrates to interact with (*S*)-proline **195** and its derivatives (for example enamines) to form enantioselectively a new C−N bond. These reactions give easy and simple access to many classes of optically active molecules with high structural diversity, such as, for example, α-AAs, α-amino alcohols, chiral heterocycles, etc. Jørgensen[202] and List[203] independently published

Scheme 20



the first organocatalytic enantioselective direct α-amination of aldehydes using (*S*)-proline **195** (Scheme 21). The first one isolated the α-amino aldehydes **196** in very good yields and very high ee's using 2 mol % of the organocatalyst in DCM at room temperature (Scheme 21, eq a). Enantiomerically enriched α-AA derivatives and oxazolidinones were also obtained from these chiral building blocks **196**.[202] However, in the second contribution, aldehydes **196** were not isolated but obtained the corresponding optically enriched amino alcohol **197** instead, after a sequential reduction step using sodium borohydride. In this last work, the results, working in acetonitrile as solvent with higher (*S*)-proline **195** charges (10 mol %) and at 0 °C, were sensibly better than those obtained by Jørgensen's group (Scheme 21, eq b).[203] Although the corresponding α-AAs were not obtained in this work, molecules **196** and **197** are potential precursors of α-AAs. The stereodiscrimination of both diastereotopic faces of the iminium salt derived from the aldehyde and proline is presumed to be assisted by a hydrogen bonding between the azo-compound and the acidic hydrogen of the carboxylic group.

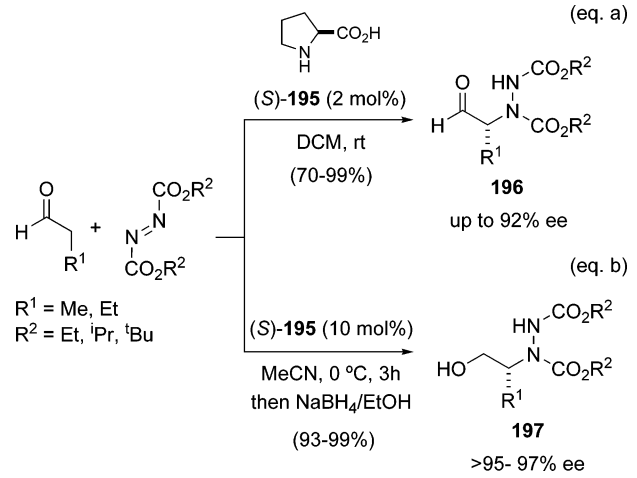
An *in situ* catalyst improvement in the proline-mediated α-amination of aldehydes has been proposed on the basis of kinetic works, which revealed that a rate enhancement of the reaction was attributed to the higher nucleophilicity of the freshly created iminium salt compared to the nucleophilicity of the proline. This effect, coupled with the amplification of the enantiomeric excess observed by these species, provided the necessary and sufficient conditions for a chemical rationalization of the origin of biological homochirality.[204] This reaction has also been performed in ionic liquids in order to study the potential of these solvents for asymmetric organocatalysis. The combination of [bmim]BF_4 as ionic liquid and (*S*)-proline **195** (5 mol %) gave the best result of the α-amino aldehyde **196**, which is comparable to that obtained under similar conditions in traditional solvents; however, the reaction rates seem to be even faster in ionic liquids.[205]

The functionalized indanecarboxaldehyde **198** was allowed to react with dibenzyl azodicarboxylate in the presence of (*S*)-proline **195** (20 mol %) in an efficient enantioselective synthesis of the metabotropic glutamate receptor ligands (*S*)-AIDA **200a** and (*S*)-APICA **200b**.[206] The intermediate

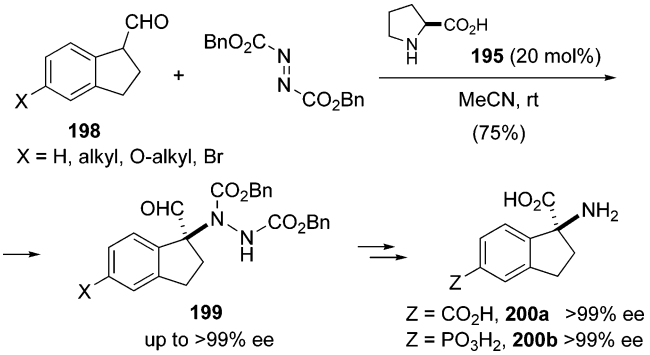
Table 15. Electrophilic Amination of α-Cyanocarboxylates 190 Using Alkyl Azodicarboxylates in the Presence of Organocatalysts 192−194

	190					product **191**			
entry	R^1	R^2	R^3	catalyst (mol %)	*T* (°C)	conv (%)	config	ee (%)	ref
1	Ar	^{t}Bu	^{t}Bu	**192** (5)	−78 to rt	>99	(*S*)	up to >98	198
2	Ph	Et	Et	**193a** (10)	rt	>99		up to 11	199
3	Ph	Et	Et	**193b** (10)	rt	>99		up to 15	199
4	Ph	Et	Et	**194** (10)	−78	>99	(*S*)	up to 85	199
5	Ph	Et	Bn	**194** (10)	−78	>99	(*S*)	up to 95	199
6	Ph	Et	^{t}Bu	**194** (10)	−78	99	(*S*)	up to 97	199
7	Ar	Et	^{t}Bu	**194** (10)	−78	>99	(*S*)	up to 99	199

Scheme 21



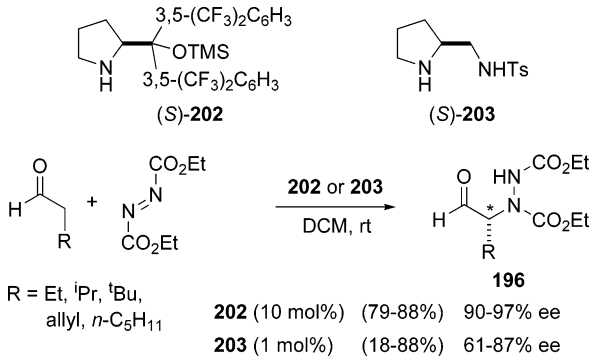
Scheme 22

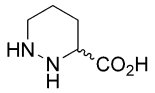


α-amino aldehyde **199** was obtained in good chemical yield and with an excellent enantioselectivity (>99% ee) (Scheme 22). This compound **199** was submitted to different reaction sequences (three or four steps) according to the nature of the X substituent and the final structure **200a** or **200b**.

Two more examples of enantioselective α-amination reaction of aldehydes promoted by (*S*)-proline **195** have been reported for the preparation of chiral α-amino aldehydes and oxazolidinones from α,α-disubstituted aldehydes[207] and for the efficient synthesis of (*R*)- and (*S*)-piperazic acids **201**, which have been found as components of naturally occurring antibiotic cyclodepsipeptides.[208] For α-branched aldehydes, the reaction catalyzed by (*S*)-proline **195** (30 mol %) afforded higher ee (up to 86%) than the reactions run in the presence of (*S*)-2-azetidinecarboxylic acid (30 mol %).[207] Nevertheless, in the synthesis of (*R*)- and (*S*)-piperazic acids **201**, the α-amino aldehyde intermediate was not isolated, obtaining the *O*-protected α-amino alcohol **197** in 92% yield and >90% ee in an analogous transformation to the previously described one in eq b of the Scheme 21, using (*S*)-proline **195** (10 mol %) and dibenzyl azodicarboxylate. The final α-AA derivative structure was obtained after four additional steps.[208]

Scheme 23



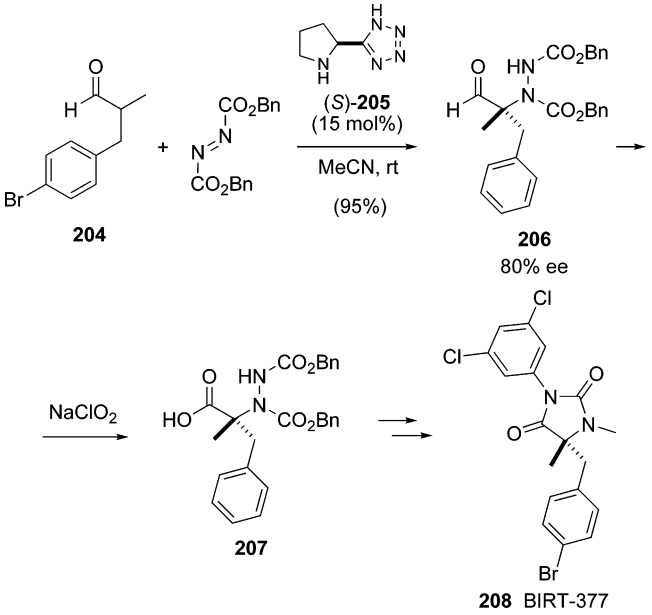


(*S*)-Proline derivatives **202**[209] and **203**[210] were tested in the enantioselective hydrazination of aldehydes, furnishing different ranges of chemical yield and enantioselection as depicted in Scheme 23. Organocatalyst (*S*)-**202** efficiently transforms aldehydes into products **196** with a wider number of substituents R; even R = ^{i}Pr and ^{t}Bu were very appropriate substrates in this reaction but using larger amounts of the catalyst (10 mol %) *versus* the 1 mol % employed in the reaction catalyzed by (*S*)-**203**.

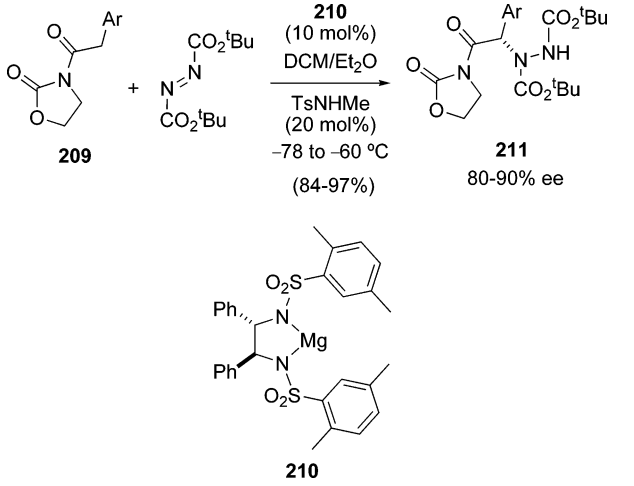
The total synthesis of the cell adhesion inhibitor BIRT-377 **208** was designed on the basis of the formation of a quaternary stereocenter through an enantioselective α-amination of the α-branched aldehyde **204** with dibenzyl azodicarboxylate.[211] To improve the enantioselection, a screening of the proline-derived catalysts and solvents was made, showing the reaction catalyzed by tetrazolylproline **205** (15 mol %), in MeCN at room temperature, to have the best enantioselectivities. The final ee reported for **206** was 80% and >99% after recrystallization of the purified samples. The obtainment of the α-AA derivative **207**, by oxidation of **206** with $NaClO_2$, was a necessary step for the synthesis of **208** (Scheme 24), which was obtained after four additional steps.[211]

At this time, the organocatalyst-mediated electrophilic amination has displaced the traditional metal-catalyzed enantioselective amination; in fact, the number of articles concerning the last topic is clearly lower, but never unimportant. The first enantioselective α-amination of an enolate catalyzed by a chiral magnesium complex was published by Evans' group in 1997.[212] The selected substrates were *N*-acyloxazolidinones **209**, which were aminated using the

Scheme 24



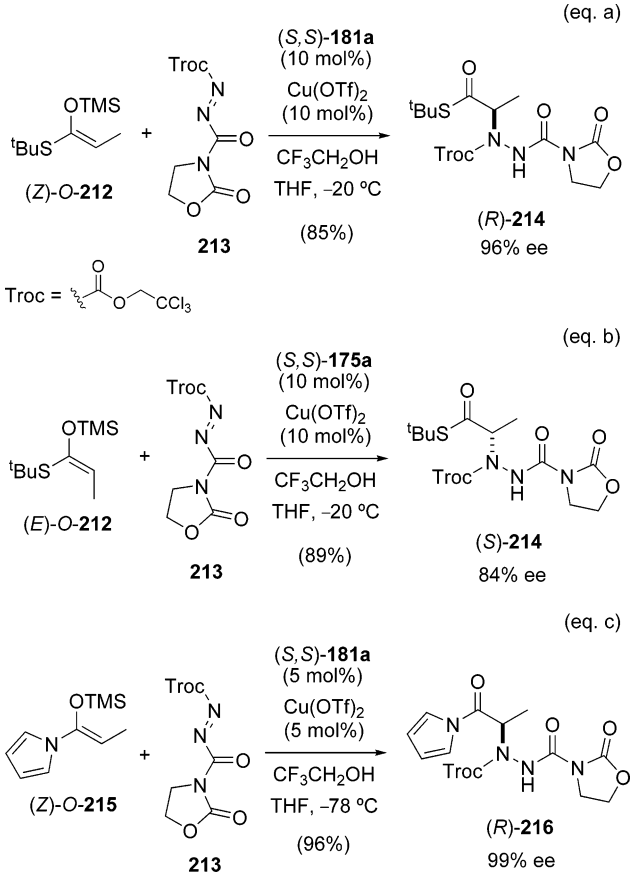
Scheme 25



chiral sulfonamide−magnesium **210** (10 mol %) and *N*-methyl-*N*-(*p*-toluene)sulfonamide (20 mol %), affording α-AA precursors **211** in high yield and very important enantiomeric excesses. These ee values were at least 99% after recrystallization of the isolated compounds under the most appropriate solvent. Upon careful kinetic analysis, the sulfonamide can accelerate the hydrazide conjugate protonation and the associated liberation of the active catalyst. That is because the catalyst turnover rather than the enolization is the rate-determining step and this reagent exhibited a first-order dependence on the reaction rate (Scheme 25).[212,213]

The Cu complex formed by the bisoxazoline ligand (*S*,*S*)-**181a** (Figure 20) (5−10 mol %) was a very efficient catalyst for the reaction of functionalized silyl ketene acetals of thioesters **212** and **215** with unsymmetrical azodicarboxylate **213**, obtaining in high yield and in very good enantioselections the products **214** and **216** (Scheme 26, eqs a and c). In this stereospecific reaction, it was also critical to use the geometrically pure enolsilanes to achieve high enantioselections because the (*Z*)-*O*-enol of thioester **212** furnished products **214** with the opposite configuration than that obtained when using the (*E*)-*O*-enol of thioester **212** (Scheme

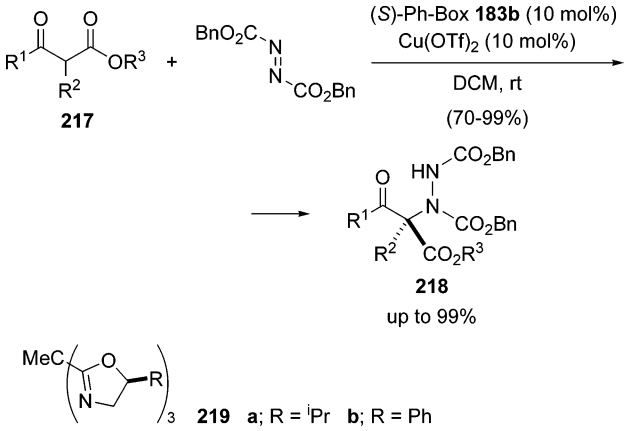
Scheme 26



26, eqs a and b). The chiral aminosulfonamide **175a** (Scheme 14) proved to be not as efficient a ligand as **181a**, for carrying out these copper-mediated transformations, as can be observed in eqs a and b of the Scheme 26. Both acylpyrrole (*R*)-**216** and the thioester hydrazino adducts (*R*)- or (*S*)-**214** were converted to several families of α-AA derivatives as α-amino thioesters or α-amino amides obtained from *tert*-butylglycine, valine, and allylglycine, using very mild reaction conditions.[214] In a similar reaction, the catalytic enantioselective α-amination of ketene acetals derived from esters and the thioester **212** with dibenzyl azodicarboxylate has also been published. The final products were obtained in excellent yields with up to 86% when the (*S*)-Binap **87a**−[Ag] complex was employed rather than other transition metals essayed.[215]

The direct α-amination of α-substituted *β*-keto esters **217** with dibenzyl azodicarboxylate as the nitrogen source was successfully developed using the (*S*)-Ph-Box **181b**−[Cu] (10 mol %) chiral catalytic complex.[216] The resulting α-amino ester derivatives **218** were obtained with excellent enantioselection, and nine of ten examples were run with more than 96% ee and very high chemical yields (Scheme 27). This identical sequence, with the same catalytic system, has been employed for the domino addition−cyclization reaction performed with substrate **217** (R^1 = Me, R^2 = CH_2CH=C=CH_2), obtaining quantitatively the corresponding product **218** with excellent enantioselectivity, whose absolute ee value was not reported. The solvent was evaporated, and immediately this hydrazine **218** was conveniently treated to yield pyrazoline derivatives, which can be considered as potential precursors of cyclic α-AA derivatives.[217a] An analogous reaction with a more sophisticated chiral trisoxazoline **219b** has been reported, furnishing the same enan-

Scheme 27



tioselectivities as those previously described for the reaction using (*S*)-Ph-Box ligand **181b** (Figure 20) (up to 99% ee).[217b]

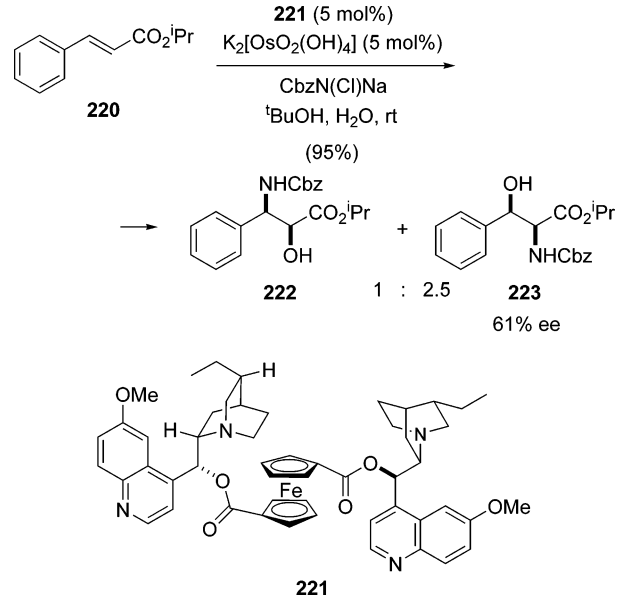
3.3. Aminohydroxylation and Diamination

In 1975 Sharpless and co-workers discovered the stoichiometric aminohydroxylation of alkenes by alkylimido Os complexes, leading to protected vicinal amino alcohols.[218] The first enantioselective version, using stoichiometric amounts of Os complexes, was reported in 1994,[219] with the original catalytic enantioselective aminohydroxylation being published in 1996.[220] The significance of this invention was evident due to the double functionalization at the two adjacent carbon atoms of the starting alkene with a total control of the absolute configuration in both of them. This reaction was part of the body of work developed by Sharpless for which he was awarded the 2001 Nobel Prize in chemistry.

This exciting reaction has been the subject of very recent reviews[221] dealing with its mechanism, its enantio- and diastereoselectivity, the effect of the substituents in the alkene, the catalyst, the nitrogen sources, etc. One of the most remarkable aspects of the asymmetric aminohydroxylation is that different ligands may be used to control the regioselectivity of this transformation. Usually, the aminohydroxylation reaction of α,*β*-unsaturated esters produces *β*-amino-α-hydroxy esters, but some catalytic systems can invert the regiochemistry to afford α-amino-*β*-hydroxy esters, which are direct precursors of *β*-hydroxy substituted α-AAs. Thus, for instance, cinnamate underwent this reversal in regioselectivity, giving the α-AA derivatives as major products under very strict reaction conditions; otherwise, *β*-amino esters are generated as major products instead.[221e,222] In the last 2 years, this particular control has been forced in many examples,[221] giving mixtures of regioisomers, as occurred in the reaction of the isopropyl cinnamate **220**. In this particular case, using the hybrid ferrocene carboxylic acid-*Cinchona* alkaloid ligand **221**, the role of the oxidating agent RN(Cl)Na was crucial in order to invert the **222**/**223** regioisomeric ratio. While chloramine-T, whose R = Ts, gave a 5/1 ratio of the mentioned products, the chloramine with R = Cbz afforded a 1/2.5 ratio of regioisomers (Scheme 28).[223] The same authors described the first detailed investigation on the stereochemical course of self-replication in the secondary cycle of the asymmetric reaction onto acrylic acid, concluding that the asymmetric self-replication is not a feasible process.[224]

Other aryl-substituted cinnamates afforded, unfortunately, low proportions of the α-AA derivatives using chloramines

Scheme 28



as stoichiometric oxidating agents and ligands $(DHQD)_2PHAL$ **224**,[225] the previous $(DHQ)_2PHAL$ **225a** in macroporous resins,[226] and the polymeric structure **226** (Figure 21), which acts under homogeneous catalytic conditions and can be removed and reused without any significant loss in its catalytic eficiency.[227]

A better alternative, based on the enantioselective aminohydroxylation of terminal alkenes, gives rise to *β*-amino primary alcohols, which can be further transformed in the corresponding α-AAs.[228] Terminal alkenes **227** underwent this regio- and enantioselective aminohydroxylation using the chiral ligand **225b** (5 mol %), isolating enantiomerically enriched primary alcohols **228** in very high chemical yields and enantiomeric ratios. The α-AA derivatives **229** were easily obtained after an additional oxidation step using a sodium chlorite/sodium hypochlorite mixture in a pH 6.7 buffered solution (Scheme 29).[228]

Acrylate or acrylic acid derivatives afforded enantiomerically enriched *β*-amino-α-hydroxy acids or esters, which are prone to undergo functional group transformations at the hydroxy moiety for the preparation of the corresponding aziridines (cyclic α-AA derivatives) in very good ee's.[229] The additional steps required to perform these transformations led us to not consider these processes here in detail.

The catalytic enantioselective diamination of alkenes[221b] is an emerging strategy to produce vicinal diamines, generating simultaneously two new stereogenic centers. In analogy with the asymmetric aminohydroxylation, the main hurdle is to find an appropriate nitrogen source able to coordinate with the Os atom to give the active bisimido complex. The first enantioselective diamination catalyzed by a Ti complex was reported by Muñiz's group using a bisimidoosmium reagent as nitrogen source (1 equiv) with the aid of a chiral Ti catalyst. The most efficient chiral complex was Taddol−Ti(IV) **231**, which gave very good enantioselectivities and excellent chemical yields of the Os complex **232**, a direct precursor of α,*β*-diamino acids (Scheme 30).[223,230,231] Therefore, the next goal in this area should be focused on the use of substoichiometric amounts of Os(VIII) species.

The procedures involving the enantioselective introduction of the α-amino group require, in general, relatively sophisticated reagents because of the low amount of species

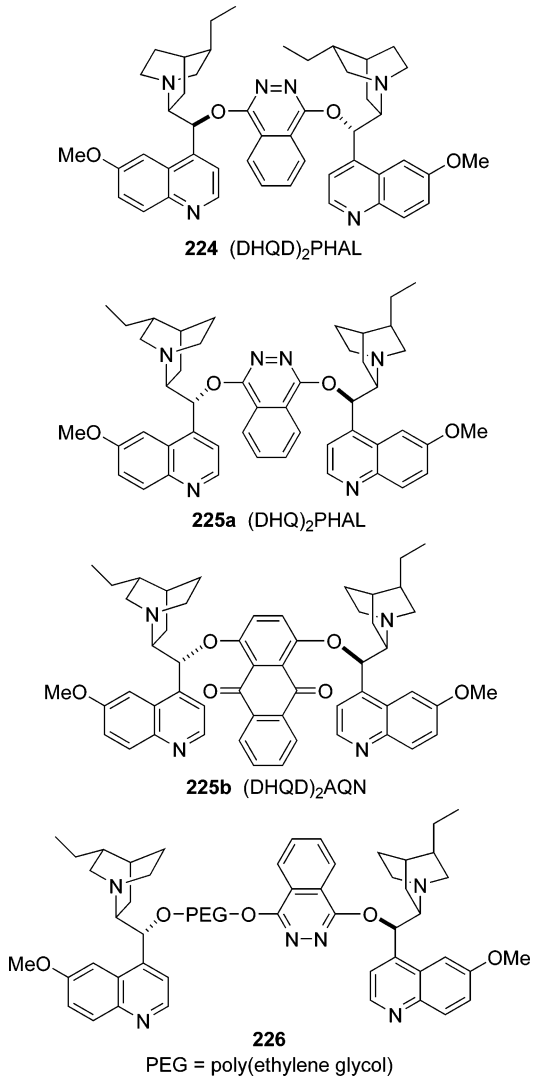
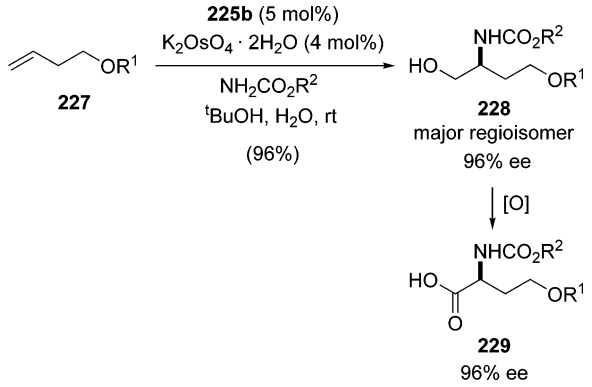


Figure 21. Catalysts **224**−**226** tested in the asymmetric aminohydroxylation of cinnamates.

Scheme 29

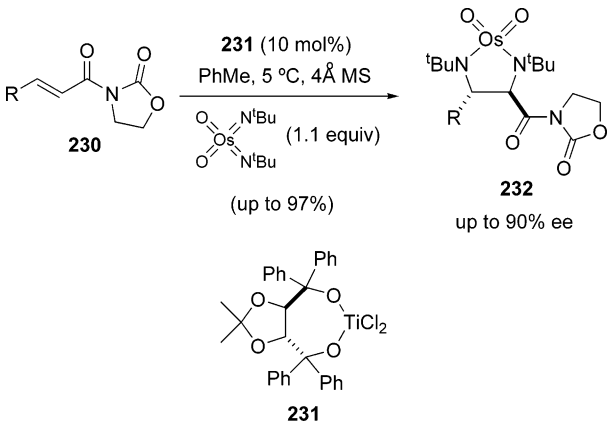


containing an electrophilic nitrogen atom. In spite of the fact that some interesting results have been published, it seems that this strategy has too many limitations and the number of reported examples is scarce in comparison with those reported in sections 2 and 4.

4. Enantioselective Introduction of the α-Side Chain

In the enantioselective introduction of the α-side chain, a very large number of strategies have been designed employing in whole examples a starting material skeleton containing a nitrogen atom placed at the α-position relative to the carboxylic group derivative. A summary of these approaches can be observed in Scheme 1 (eqs i−n), where, in many cases, several stereogenic centers are generated in the same step. Electrophilic alkylations of glycine derivatives, nucleophilic alkylations of α-imino esters, cyclopropanations, and cycloaddition reactions constitute the main transformations used for the construction of the α-side chain.

Scheme 30

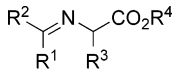


4.1. Electrophilic Alkylations of Glycine or Derivatives

In this section, the enantioselective electrophilic alkylations of enolates derived from iminic α-amino acid esters (Scheme 1, eq i) onto several electrophiles will be discussed. The main feature of these nucleophiles is based on the high acidity of the α-hydrogens. In this way, the corresponding imino glycinates, alaninates, or other related structures can be deprotonated very mildly, thus favoring the strong interaction enolate−organocatalyst at temperatures ranging from −78 °C to room temperature. This reaction has been considered as one of the most reliable routes to obtain enantiopure α-AA derivatives. If we take a look at the review of Duthaler, published in 1994,[3x] we realize that nowadays the preferred strategy to obtain these optically pure substances is to use enantiomerically enriched organocatalysts or chiral−metal complexes (both in substoichiometric amounts) instead of using diastereoselective synthesis employing chiral glycine or chiral α-substituted glycine templates.

4.1.1. Organocatalyst-Promoted Electrophilic Additions

Chiral phase-transfer catalysts (CPTCs)[232] are able to form an ion-pair with the imino ester enolate derived from **233**, facilitating the transfer of a molecule or ion from one reaction phase to another. The most efficient and commonly used CPTC agents are enantiomerically enriched quaternary ammonium salts.[3c,e,f,l,o,232,233]



The imines **233** can be easily alkylated using relative small amounts of catalyst under mild reaction conditions (Scheme 1, eq i), simple reaction procedures, and safe and inexpensive reagents and solvents. These points and the possibility of conducting reactions on either small or large scale make this

methodology exciting and attractive. A variety of inexpensive and mild basic agents (e.g., NaOH, KOH, K_2CO_3), either in aqueous solution (liquid−liquid PTC) or as solids (solid−liquid PTC), can be used in conjunction with the selected CPTC agent. An important aspect of the alkylation reactions of ketimines **233** (R^1 and $R^2 \neq H$, $R^3 = H$) is the selective formation of only monoalkylated products (precursors of α-alkyl AAs) without concomitant production of the undesired α,α-dialkylated compounds. However, aldimines **233** (R^3 and $R^2 \neq H$, $R^1 = H$) are prone to give the α,α-dialkylated AAs under these reaction conditions in high chemical yields. In both cases, the electrophiles employed are mainly activated halogenides such as benzylic, allylic, propargylic, or alkyl iodides or bromides. Electrophilic olefins and aldehydes are also suitable electrophiles in the corresponding Michael-type addition and aldol reactions, respectively. The obtainment of the enantiomerically pure α-AAs can be accomplished by the hydrolysis of the imino and ester groups using a mild acidic solution, hydrogenolysis, or transimination, and the careful control of these hydrolysis conditions allows the desired deprotection in the presence of other functionalities.

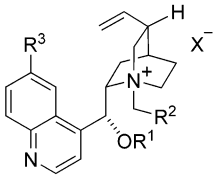
Since the pioneering work of O'Donnell in 1989,[234] the asymmetric synthesis of α-AAs by enantioselective PTC electrophilic substitution of enolates onto electrophiles has gained an impressive departure from the previous results obtained independently by Lygo[235a] and Corey[235b] in terms of enantioselectivity and general applicability of the *Cinchona*-derived quaternary ammonium salts. Despite multiple attempts to elaborate new chiral quaternary ammonium salts, only the rigid spiranic ammonium salts, derived from chiral Binol, developed in 1999 by Maruoka[236] emerged as a competitive and very promising alternative to the related *Cinchona* derived catalysts. At this moment, it is fair to say that the two main families of quaternary ammonium salts operating with very high efficiency and general applicability are the *Cinchona* alkaloid derivatives and the spiro ammonium salts derived from the two chiral Binol forms.

4.1.1.1. Cinchona Alkaloid Derived Organocatalysts. These chiral ammonium salts can be easily obtained from the natural source through very simple chemical transformations.[3c,e,f,l,o,232,233] The more relevant examples of these catalysts, published in the last 3 years, dealing with the enantioselective introduction (alkylation at the α-position) of the side chain of the α-AA using nonpolymeric ammonium salts derived from *Cinchona* alkaloids such as cinchonine, cinchonidine, quinine, and quinidine, are shown in Figure 22, although on a few occasions these alkaloids can be employed themselves for alkylation reactions.

On the other hand, the simple preparation and high acidity of the α-imino esters **233**, obtained by condensation of the α-amino esters with aldehydes or ketones, allowed the enantioselective preparation of the titled α-AA derivatives. Thus, compounds **233** were treated with the mentioned catalytic salts in aqueous basic media and in the presence of the alkylating agent (normally an activated alkyl halide), yielding α-substituted enantiomerically enriched glycines or α-carbon quaternized α-AA derivatives **248** (Table 16). Interestingly, an opposite sense of the asymmetric induction can be observed by changing the alkaloid; thus, for example, the cinchonidine arrangement induces a (*S*)-absolute configuration in the newly created stereogenic center of **233** while the cinchonine (also called the pseudoenantiomer of the cinchonidine) skeleton induces a (*R*)-absolute configuration in the same transformation. In Figure 22 are represented the ammonium salts containing a unit of natural *Cinchona* alkaloid (**234**−**237**), a second group of chiral bases bearing a unit of alkaloid as well (**238**−**240**), which are precursors of chiral ammonium salts, and, finally a block of ammonium salts incorporating two or more alkaloid units (**241**−**247**). While ammonium salts **234**−**237** and **241**−**247** gave very interesting results in alkylation reactions of imino esters **233**, modified alkaloids **238**−**240** gave very low enantioselections in the mentioned reaction, demonstrating the benefits of using these chiral PTC agents rather than their corresponding free bases.

From the examples depicted in Table 16 it can be observed that cinchonidinium salts, particularly, the anthracenyl derivative **234c** (entries 5−8) and **234n** (entries 12−17), are the most extensively applied catalysts in the alkylation reactions of imino esters **233** using inexpensive bases as NaOH or KOH and CsOH, respectively. The optimal temperature in most cases can be considered low, mainly from −78 °C for CsOH to 5 °C for NaOH. With the aim to improve these results, the new catalysts (Figure 22) have been developed using 5−10 equiv of the corresponding activated alkylating agent. Chiral PTC catalysts **235j**−**k** were tested in the alkylation of the alanine imino ester **233a**, resulting in a more appropriate catalytic system when benzyl bromides were selected as electrophiles (Table 16, entries 1 and 2).[237] The chiral *trans*-stilbene α-AAs, derived from compound **233b**, after alkylation with bromide **249** (Figure 23), could bind to antibodies 19G2, but only the (*S*)-form-19G2 aggregate afforded a blue fluorescence, which can act as a sensor of the optical purity of an enriched mixture of such α-AAs.[238] This property was successfully evaluated in the determination of the enantiomeric ratio of the products obtained from a library of 40 different alkaloid ammonium salts, **234**−**237** and **242b**, with the last one being the most efficient catalyst (Table 16, entry 3).[238] Two groups published independently their results concerning the employment of the cinchonidinium salt **234c** during the enantioselective alkylation of ketimine **233c** using water as solvent at temperatures ranging from 0 to 5 °C. The results obtained were very similar to each other, including the good ee's (Table 16, entries 4−8).[239,240] Moreover, a series of the same chiral catalysts **234a**, **d**, **e**, **f**, **g**, and **o** were designed for evaluating the influence of the aryl substituents in the benzylic moieties of them, detecting a notable improvement of the enantioselection when using chiral salt **234g** at −20 °C (Table 16, entries 9−11).[241]

The incorporation of the labeled atoms from bromides **250** and **251** (Figure 23) onto the α-AA framework was required for the preparation of [^{18}F]fluoro-L-dopa **262** (a very important radiopharmaceutical for positron emission tomography, Figure 24)[242] and isotopomers of methionine, selenomethionine, cysteine, and selenocysteine.[243] In both examples, the catalyst **234n** (*O*-allyl, *N*-anthracenylmethyl, 350 mol % or 5 mol %) was used at 0 °C using CsOH or KOH as base, respectively (Table 16, entries 12−14). This enantioselective alkylation is a key step in numerous total syntheses of natural and biologically interesting molecules. Thus, antibacterial biphenomicin B (**264**, Figure 24) and the antitumor agent ecteinascidin-743 were elaborated using α-AAs prepared (for example **263**, Figure 24) by means of catalyst **234n** and bromides **253** or **254** (Figure 23), respectively, for the alkylation of **233c** at very low temperatures (Table 16, entries 15 and 16).[244,245] Chiral PTC



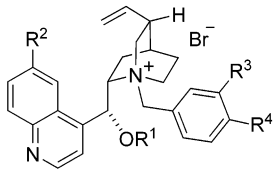
234

a; $R^1 = R^3 = H$, $R^2 = Ph$, X = Cl
b; $R^1 = R^3 = H$, $R^2 = Ph$, X = Br
c; $R^1 = R^3 = H$, R^2 = 9-anthracenyl, X = Cl
h; R^1 = Me, R^2 = 9-anthracenyl, $R^3 = H$, X = I
i; R^1 = allyl, $R^2 = Ph$, $R^3 = H$, X = H
j; R^1 = allyl, $R^2 = 2,3,4\text{-}F_3C_6H_2$, $R^3 = H$, X = Br
k; R^1 = allyl, R^2 = 1-naphthyl, $R^3 = H$, X = Br
l; R^1 = allyl, R^2 = 2-naphthyl, $R^3 = H$, X = Br
m; R^1 = allyl, R^2 = 9-anthracenyl, $R^3 = H$, X = Cl
n; R^1 = allyl, R^2 = 9-anthracenyl, $R^3 = H$, X = Br
p; R^1 = Bn, $R^2 = Ph$, $R^3 = H$, X = Br
q; R^1 = Bn, R^2 = 9-anthracenyl, $R^3 = H$, X = Br
r; $R^1 = 4\text{-}(C_{12}H_{25})C_6H_4$, $R^2 = R^3 = H$, X = Br
s; $R^1 = H$, R^2 = 2-pyridyl, $R^3 = H$, X = Cl

t; $R^1 = R^3 = H$, X = Cl, R^2 =

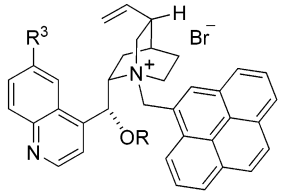
u; $R^1 = R^3 = H$, X = Cl, R^2 =

v; $R^1 = R^3 = H$, X = Cl, R^2 =



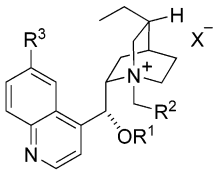
234

d; $R^1 = R^2 = R^3 = H$, $R^4 = C(OH)Ph_2$
e; $R^1 = R^2 = R^3 = H$, $R^4 = C(OH)(1\text{-naphthyl})_2$
f; $R^1 = R^2 = R^4 = H$, $R^3 = C(OH)Ph_2$
g; $R^1 = R^2 = R^4 = H$, $R^3 = C(OH)(1\text{-naphthyl})_2$
o; R^1 = allyl, $R^2 = R^4 = H$, $R^3 = C(OH)$(1-naphthyl)



234

w; R = H **x**; R = allyl



235

a; $R^1 = R^3 = H$, $R^2 = Ph$, X = Cl
b; $R^1 = R^3 = H$, R^2 = 2-pyridyl, X = Cl

c; $R^1 = R^3 = H$, X = Cl, R^2 =

d; $R^1 = R^3 = H$, X = Cl, R^2 =

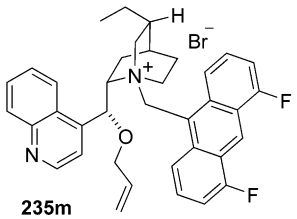
e; $R^1 = R^3 = H$, X = Cl, R^2 =

f; $R^1 = R^3 = H$, $R^2 = 2,3,4\text{-}F_3C_6H_2$, X = Br
g; R^1 = allyl, $R^2 = Ph$, $R^3 = H$, X = Br

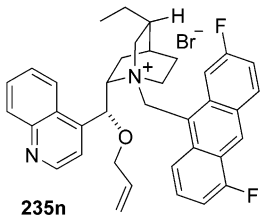
h; R^1 = allyl, $R^3 = H$, X = Br, R^2 =

i; R^1 = allyl, $R^3 = H$, X = Br, R^2 =

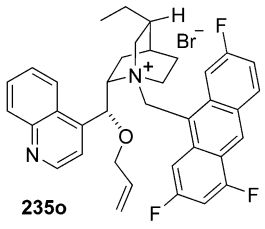
j; R^1 = allyl, $R^2 = 2,3,4\text{-}F_3C_6H_2$, $R^3 = H$, X = Br
k; R^1 = allyl, R^2 = 9-anthracenyl, $R^3 = H$, X = Br
l; R^1 = Bn, R^2 = 9-anthracenyl, $R^3 = H$, X = Br



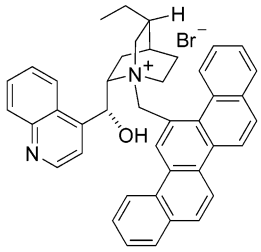
235m



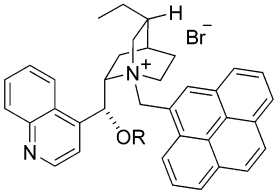
235n



235o

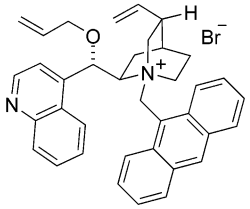


235p

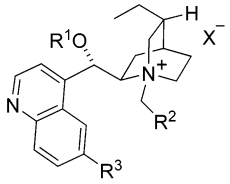


235

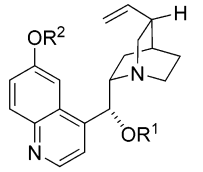
q; R = H
r; R = allyl
s; R = 9-anthracenyl



236

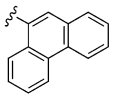


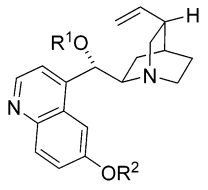
237



238

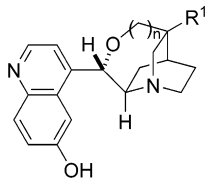
a; R^1 = H, R^2 = Me (quinine)
b; R^1 = Bn, R^2 = H
c; R^2 = H, R^1 =





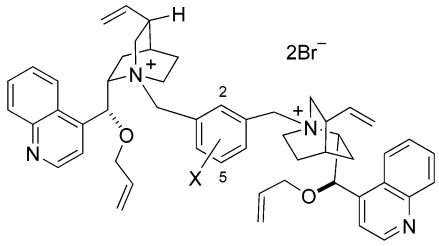
239

a; R^1 = H, R^2 = Me (quinidine)
b; R^1 = Bn, R^2 = H

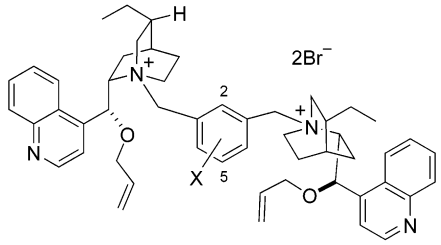


240

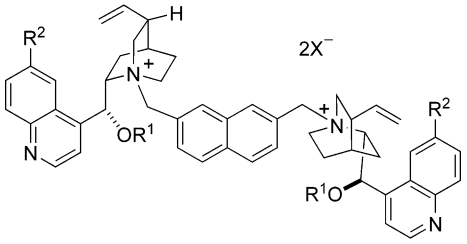
a; R^1 = $CH{=}CH_2$, n = 0
b; R^1 = H, n = 2
192 (β-ICD) R^1 = Et, n = 0



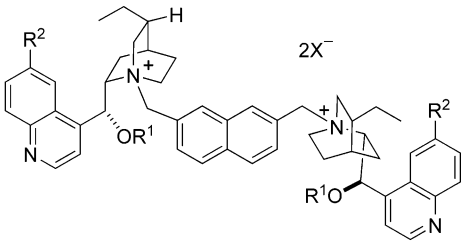
241a



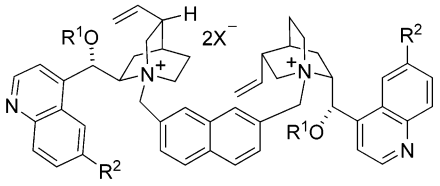
241b



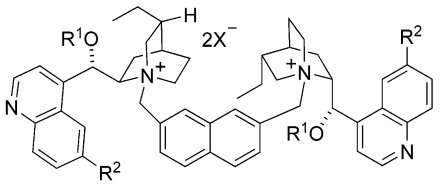
242a



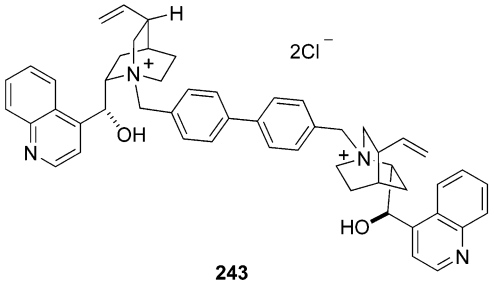
242b



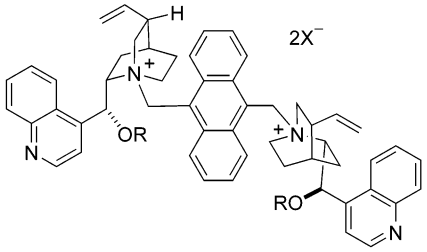
242c



242d



243



244

a; R = H, X = Cl
b; R = H, X = BF_4
c; R = H, X = PF_6
d; R = allyl, X = Br
e; R = allyl, X = BF_4
f; R = allyl, X = PF_6

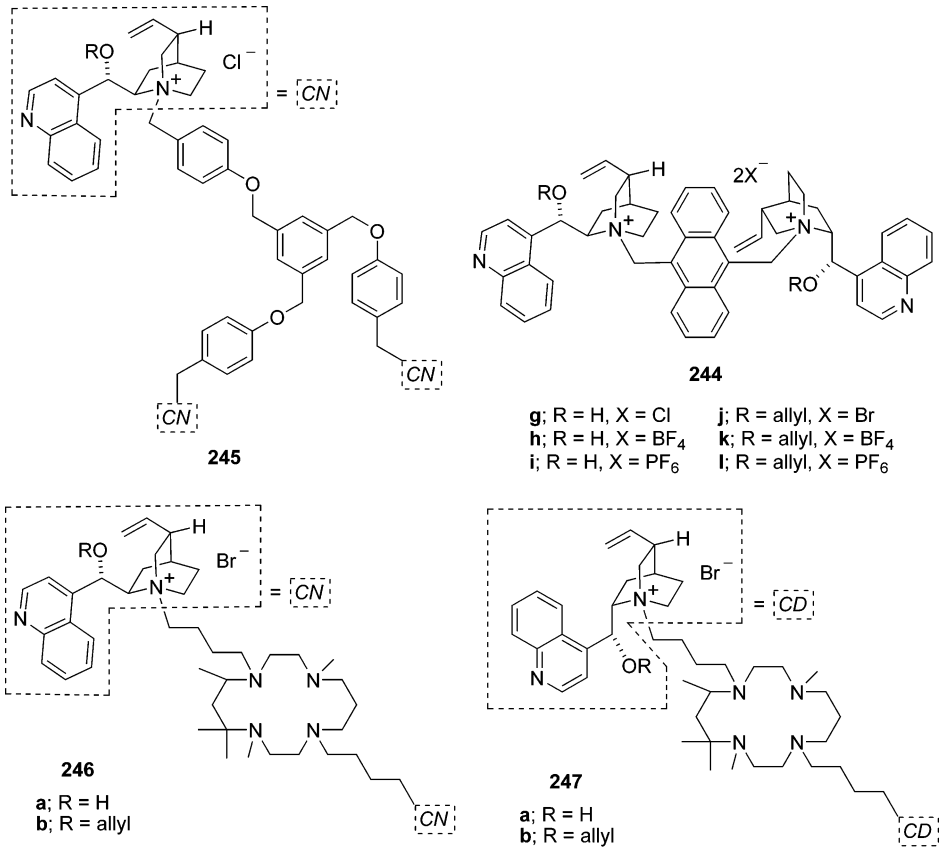


Figure 22. Organocatalysts employed for the enantioselective alkylation of imino esters **233**.

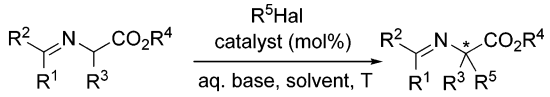
catalysts **235j** and **235l** (10 mol %) were efficiently employed in the synthesis of α-AAs, which were precursors of a central tryptophan residue **265** (Figure 24) of celogentin C, an inhibitor of the polymerization of the tubulin (Table 16, entry 26),[250] and neodysiherbaine **267** (Figure 24), a potent natural excitatory α-AA agent (Table 16, entry 28).[252] Chiral dimeric ligand series with a naphthalene bridge **242** proved to be very effective catalysts in the stereoselective alkylations (96% ee) of compound **233c** with bromides **260** and **261** at 0 °C (Figure 23 and Table 16, entries 38 and 39) during the total synthesis of the alkaloid (−)-antofine[256] and the depsipeptide cryptophycin-3,[257] two potent antitumor agents. Particularly, the α-AA derivative **268** (Figure 24) prepared from **261** was the key intermediate in the synthesis of the already mentioned cryptophycin-3. Chiral cinchonidinium salt **234n** (*O*-allyl, *N*-anthracenylmethyl) was also suitable, together with the related cinchonine **236**, for the practical preparation of (*R*)- and (*S*)-7-azaindoline α-AA[246] and an α-AA containing a 3,4-dihydro-1*H*-quinolin-2-one, **270** (Figure 24) (Table 16, entries 17−20).[247] Other dihydrocinchonidine **235** chiral ammonium salts such as **235h**, **i**, **k**, and **m** were the most important catalysts of their corresponding series in the general studies of the alkylation of **233c** with several activated halides for many interesting purposes (Table 16, entries 21−25 and 27),[248,249,251] especially in the synthesis of α-aroylalanine derivatives.[251]

Dihydrocinchonidinium derivatives **235p**−**s**, bearing aromatic polycyclic moieties at the nitrogen atom, were essayed in the synthesis of α-AAs, with organocatalyst **235q** giving the best results working at room temperature (Table 16, entries 29−31).[253] As well as the fluorine atoms in the alkylation of the quinuclidine skeleton in entries 21 and 22, the presence of a *o*-fluoro-dimeric *Cinchona*-derived PTC was also considered, but the final electronic effect only was shown for the examples run with catalyst **241b** (Table 16, entries 32−34).[254] Presumably, the aromatic fluorine atom would participate in an internal hydrogen bonding involving water in order to maintain a more rigid conformation.

Benzophenone-derived glycine Schiff base **233c** was enantioselectively alkylated with allylic and benzylic bromides as well as alkyl iodides in the presence of dimeric chiral salts **242b** and **234c**, although, on this occasion, the first one was more efficient than the latter when a solid support preloaded with a base (kaolin/KOH) was employed (Table 16, entries 35−37).[255] A deeper survey of a large number of electrophiles was documented for the enantioselective alkylation of **233c** mediated by dimeric chiral PTC agents **244a**−**l** at 0 °C, which were precipitated in ether and further reused in a new reaction without loss of efficiency (Table 16, entries 40−45). Both enantiomers **248** could be selectively isolated by the use of a cinchonine or a cinchonidine derivative **244** without any noticeable effect when the halide anion of the quaternary ammonium salt was replaced by BF_4^- or PF_6^-.[258] The new trimeric *Cinchona* alkaloid **245** and the dimeric structure **246** and **247** (Table 16, entries 46−48 and 49−52) provided good enantioselectivities of the resulting products **248** in the reactions run at 0 or −10 °C, respectively.[259,260] However, the smallest amount of the catalysts recorded in the Table 16 corresponded to the chiral PTC agents **246** and **247** (1.5 mol %), bearing two cinchonine or two cinchonidine units, respectively, with a long distance between them.[260]

In Figure 25 we can observe the current strategies followed in the new design of polymeric *Cinchona* alkaloid derived catalysts. In fact, the four alternatives can be readily applied, even the option to anchor the polymer to the quinoline moiety

Table 16. Enantioselective Alkylation of α-Amino Esters 233 Mediated by Organocatalysts 234−247



233 **248**

a; R^1 = H, R^2 = 1-naphthyl, R^3 = Me, R^4 = ^{t}Bu
b; R^1 = R^2 = Ph, R^3 = H, R^4 = Me
c; R^1 = R^2 = Ph, R^3 = H, R^4 = ^{t}Bu

							product **248**			
entry	**233**	catalyst (mol %)	R^5-Hal	base	solvent	*T* (°C)	yield (%)	config	ee (%)	ref
1	**233a**	**235j** (10)	RCH_2-Br[a]	RbOH	PhMe	−35	up to 89	(*S*)	up to 85	237
2	**233a**	**235j** (10)	$ArCH_2$-Br	RbOH	PhMe	−35	up to 93	(*S*)	up to 96	237
3	**233b**	**242b** (−)[b]	**249**	KOH	PhMe/$CHCl_3$	0	85	(*S*)	83	238
4	**233c**	**234c** (1)	alkyl-I	KOH	H_2O	0	up to 83	(*S*)	up to 92	239
5	**233c**	**234c** (1)	RCH_2-Br[a]	KOH	H_2O	0	up to 87	(*S*)	up to 90	239
6	**233c**	**234c** (1)	$ArCH_2$-Br	KOH	H_2O	0	up to 97	(*S*)	up to 91	239
7	**233c**	**234c** (1)	RCH_2-Br[a]	KOH	H_2O	5	up to 60	(*S*)	up to 92	240
8	**233c**	**234c** (1)	Bn-Br	KOH	H_2O	5	>98	(*S*)	87	240
9	**233c**	**234g** (10)	alkyl-I	KOH	PhMe/$CHCl_3$	−20	up to 78	(*S*)	up to 94	241
10	**233c**	**234g** (10)	RCH_2-Br[a]	KOH	PhMe/$CHCl_3$	−20	up to 92	(*S*)	up to 93	241
11	**233c**	**234g** (10)	$ArCH_2$-Br	KOH	PhMe/$CHCl_3$	−20	up to 93	(*S*)	up to 92	241
12	**233c**	**234n** (350)	**250a**,**b**	CsOH	PhMe	0	>90	(*S*)	>95	242
13	**233c**[c]	**234n** (5)	**251**	KOH	PhMe	0	90	(*S*)	>90	243
14	**233c**[c]	**234n** (5)	**252**	KOH	PhMe	0	70	(*S*)	>90	243
15	**233c**	**234n** (10)	**253**	CsOH	DCM/H_2O	−50	87	(*S*)	>95	244
16	**233c**	**234n** (10)	**254**	CsOH	DCM	−78	>87	(*S*)	>98	245
17	**233c**	**234n** (10)	**255**	CsOH	DCM	−60	87	(*S*)	89	246
18	**233c**	**236a** (10)	**255**	CsOH	DCM	−60	77	(*R*)	>99	246
19	**233c**	**234n** (10)	**256**	CsOH	DCM	−30	92	(*S*)	93	247
20	**233c**	**236a** (10)	**256**	CsOH	DCM	−30	90	(*R*)	90	247
21	**233c**	**235m** (10)	Me-I	KOH	PhMe/$CHCl_3$	−40	66	(*S*)	97	248
22	**233c**	**235m** (10)	RCH_2-Br[a]	KOH	PhMe/$CHCl_3$	−40	up to 92	(*S*)	98	248
23	**233c**	**235h**,**i** (10)	*n*-C_6H_{13}-I	KOH	PhMe/$CHCl_3$	−20	72−80	(*S*)	>99	249
24	**233c**	**235h**,**i** (10)	RCH_2-Br[a]	KOH	PhMe/$CHCl_3$	−20	92−97	(*S*)	up to 98	249
25	**233c**	**235h**,**i** (10)	$ArCH_2$-Br	KOH	PhMe/$CHCl_3$	−20	85−96	(*S*)	98−99	249
26	**233c**	**235j** (10)	**257**	KOH	PhMe/$CHCl_3$	−50	80	(*S*)	90	250
27	**233c**	**235k** (10)	**258**	KOH	PhMe/DCM	rt	>75	(*S*)	94	251
28	**233c**	**235l** (10)	**259**	KOH	PhMe	rt	>93	(*S*)	>98	252
29	**233c**	**235q** (5)	alkyl-I	NaOH	H_2O	rt	88−94	(*S*)	up to 79	253
30	**233c**	**235q** (5)	RCH_2-Br[a]	NaOH	H_2O	rt	94	(*S*)	93	253
31	**233c**	**235q** (5)	$ArCH_2$-Br	NaOH	H_2O	rt	86−91	(*S*)	up to 90	253
32	**233c**	**241** (5)	*n*-C_6H_{13}-I	KOH	PhMe/$CHCl_3$	−20	81	(*S*)	>99	254
33	**233c**	**241** (5)	RCH_2-Br[a]	KOH	PhMe/$CHCl_3$	−20	92−94	(*S*)	98	254
34	**233c**	**241** (5)	$ArCH_2$-Br[d]	KOH	PhMe/$CHCl_3$	−20	90−94	(*S*)	up to >99	254
35	**233c**	**242b** (2−10)	alkyl-I	KOH[e]	PhMe/$CHCl_3$	20	78−80	(*S*)	up to 93	255
36	**233c**	**242b** (2−10)	allyl-Br	KOH[e]	PhMe/$CHCl_3$	20	88	(*S*)	up to 89	255
37	**233c**	**242b** (2−10)	$ArCH_2$-Br	KOH[e]	PhMe/$CHCl_3$	20	up to 95	(*S*)	up to 97	255
38	**233c**	**242b** (2)	**260**	NaOH	PhMe/$CHCl_3$	0	97	(*S*)	96	256
39	**233c**	**242d** (1)	**261**	KOH	PhMe/$CHCl_3$	0	87	(*R*)	96	257
40	**233c**	**244a**−**f** (5)	*n*-C_6H_{13}-I	KOH	PhMe/$CHCl_3$	0	up to 83	(*S*)	up to 86	258
41	**233c**	**244a**−**f** (5)	allyl-Br	KOH	PhMe/$CHCl_3$	0	up to 98	(*S*)	up to 90	258
42	**233c**	**244a**−**f** (5)	^{t}BuO_2CCH_2-Br	KOH	PhMe/$CHCl_3$	0	up to 67	(*S*)	up to 86	258
43	**233c**	**244g**−**l** (5)	allyl-Br	KOH	PhMe/$CHCl_3$	0	up to 97	(*R*)	up to 86	258
44	**233c**	**244a**−**f** (5)	$PhCH_2$-Br	KOH	PhMe/$CHCl_3$	0	up to 98	(*R*)	up to 88	258
45	**233c**	**244n,g**−**l** (5)	$PhCH_2$-Br	KOH	PhMe/$CHCl_3$	0	up to 91	(*R*)	up to 88	258
46	**233c**	**245** (5)	Me−I	NaOH	PhMe/$CHCl_3$	−10	up to 92	(*S*)	up to 95	259
47	**233c**	**245** (5)	RCH_2-Br[a]	NaOH	PhMe/$CHCl_3$	−10	up to 96	(*S*)	up to 90	259
48	**233c**	**245** (5)	$ArCH_2$-Br	NaOH	PhMe/$CHCl_3$	−10	up to 97	(*S*)	up to 98	259
49	**233c**	**246a**,**b** (1.5)	RCH_2-Br[a]	NaOH	PhMe/$CHCl_3$	−10	up to 98	(*R*)	up to 95	260
50	**233c**	**247c**,**d** (1.5)	RCH_2-Br[a]	NaOH	PhMe/$CHCl_3$	−10	up to 98	(*S*)	up to 97	260
51	**233c**	**246a**,**b** (1.5)	$ArCH_2$-Br	NaOH	PhMe/$CHCl_3$	−10	up to >99	(*R*)	up to 99	260
52	**233c**	**247c**,**d** (1.5)	$ArCH_2$-Br	NaOH	PhMe/$CHCl_3$	−10	up to 98	(*S*)	up to 98	260

[a] Allylic and propargylic bromides. [b] Not reported. [c] ^{14}N labeled and also ^{13}C labeled at the carbonyl group and at the α-carbon. [d] Including 2-chloromethylnaphthalene. [e] Kaolin/KOH.

through a previous demethylation of the quinine or quinidine precursor.

Polymer-supported chiral catalysts derived from *Cinchona* alkaloids have been designed for this type of chemistry, and the most relevant recent examples are illustrated in Figure 26. Their development was focused on the possible implementation of these enantioselective catalysts in large-scale processes, due to their easy separation from the reaction mixture and their feasible recycling. In general, the reactions were performed at 0 °C and using benzylic or allylic bromides as electrophiles. Chiral cinchonidine (*O*-4-nitrobenzoyl) catalyst **271**, supported on a styrene−divinylbenzene

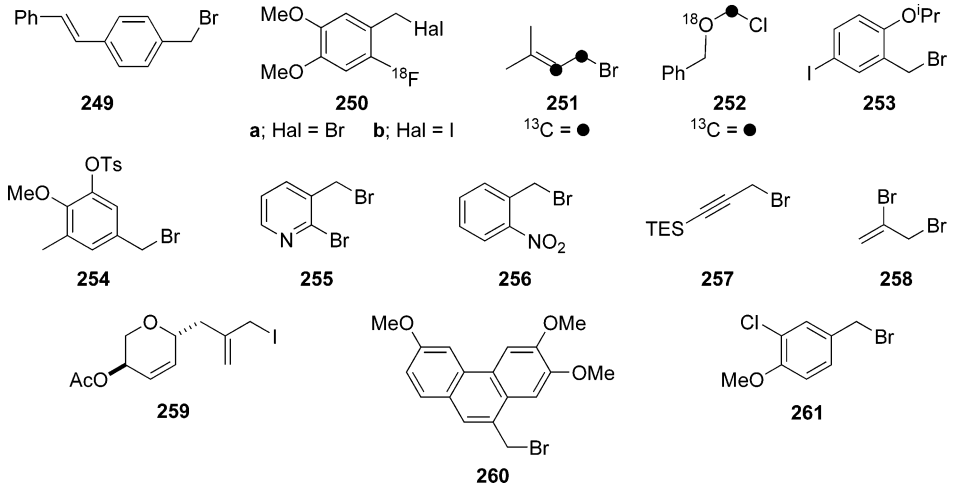


Figure 23. Uncommon alkylating agents used in the enantioselective alkylation of imino esters **233**.

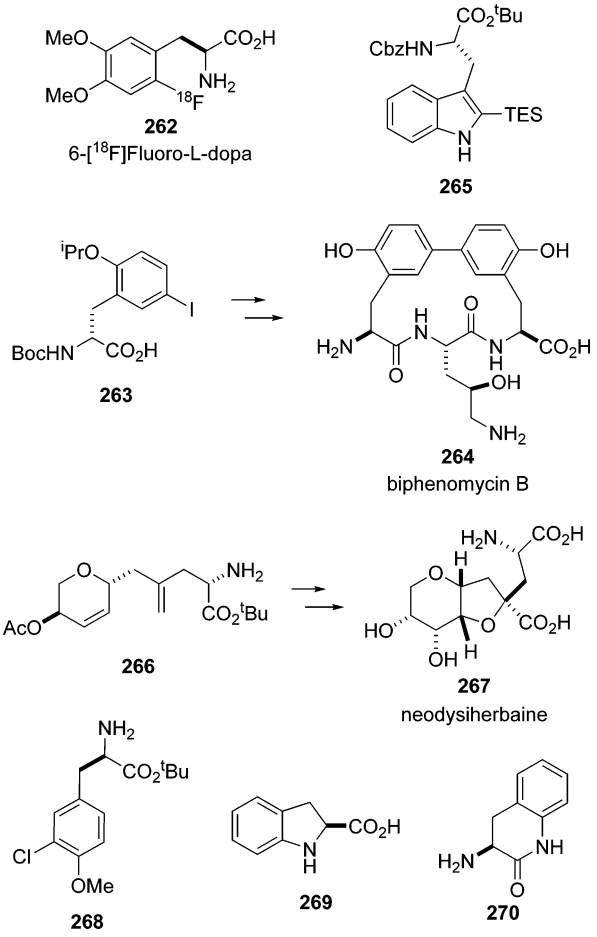


Figure 24. Some interesting α-AAs obtained by enantioselective PTC.

copolymer at the nitrogen atom, gave very poor enantioselectivities (up to 18%) of the alkylated compounds using water as solvent.[240] The poly(ethylene glycol) (PEG)-supported chiral quaternary ammonium salts **272a**−**c** gave modest to low ee's of the resulting α-AA derivatives **248** (up to 73% ee) in the exclusive examples run at room temperature (Table 17, entries 1 and 2).[261] Chiral supported catalysts **272a**,**d**, **273a**−**d**, **274**, and **275** were evaluated in the benzylation reaction of the Schiff base **233**, obtaining modest to good enantioselectivity in the synthesis of α-AA derivatives **248**. Recoverable catalyst bonded to a PEG chain **272a** (*N*-benzylated) and **274b** (*O*-benzylated), operating

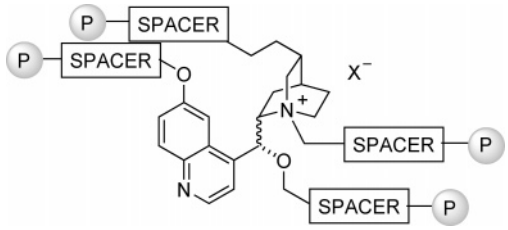
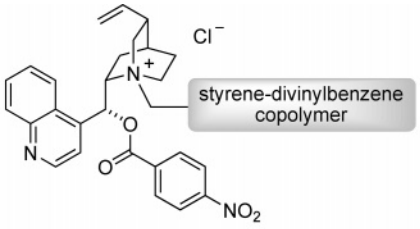


Figure 25. Current options for anchoring ammonium derivatives of *Cinchona* alkaloids to polymers.

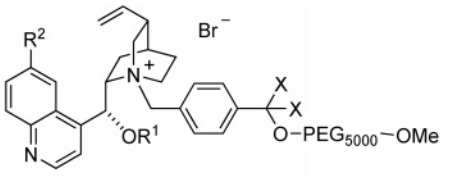
under different reaction conditions, offered the highest enantioselections at low temperatures (Table 17, entries 3−5).[262] Other different poly(ethylene glycol) immobilized *Cinchona* alkaloids, such as **276** and **277**, gave very poor results, affording a 64% ee when the α-benzylation of **233c** was performed with chiral *O*-supported organocatalyst **277b** and $CsOH·H_2O$ as base at −78 °C (Table 17, entry 6).[263]

The Merrifield resin, cross-linked with 1% of divinylbenzene, was selected as polymer for anchoring cinchonidine and cinchonine, **278** and **270**, respectively. A comprehensive study of the optimization of the α-benzylation reaction of imino esters **233c**,**d** and **e** was made, and these conditions extended to the α-alkylation reactions of the more suitable substrate **233c** (benzophenone *tert*-butyl ester) with several activated halogenides. The best enantioselections (up to 90% ee) were achieved with the chiral polymer-supported catalysts **278a** with sodium hydroxide at 0 °C and using benzylic bromides (Table 17, entries 7−8).[264] The commercially available chloromethylated polystyrene-grafted polypropylenes (chloromethylated Synphase Lanterns) were used for the *N*-quaternization of cinchonidine and cinchonine, affording polymeric ammonium salts **280** and **281**, respectively. The benzylation of the imino ester **233e** was achieved with the same degree of asymmetric induction as when using the polymers **278** and **279** at room temperature. These "Lanterns" were tweezers-separated after the reaction and reused up to three times with almost no loss of activity.[264]

Polymers **272**, **273**, and **282**−**291** were elaborated by Cahard's group and tested in the reaction of the α-benzylation of the same glycine derivative **233c**. The wide series of results contained in this contribution can be summarized as follows: (a) the cinchonidine-*N*-PEG derivative ligand **272a** was a more efficient chiral catalyst than the other polymer-supported catalysts, **272** and **273** (Table 17, entry 10); (b) identical results were achieved with macromolecules **285a**

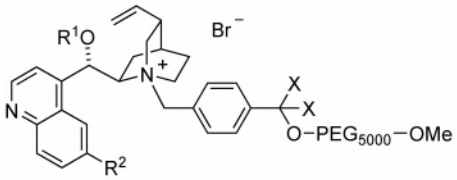


271



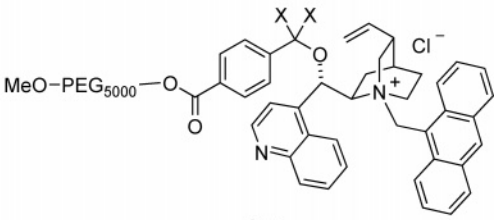
272

a; $R^1 = R^2 = X = H$ **c**; $R^1 = Bn$, $R^2 = X = H$
b; $R^1 = allyl$, $R^2 = X = H$ **d**; $R^1 = H$, $R^2 = OMe$, $X = O$



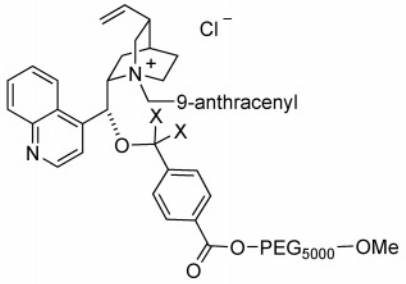
273

a; $R^1 = R^2 = X = H$ **c**; $R^1 = Bn$, $R^2 = X = H$
b; $R^1 = allyl$, $R^2 = X = H$ **d**; $R^1 = H$, $R^2 = OMe$, $X = O$



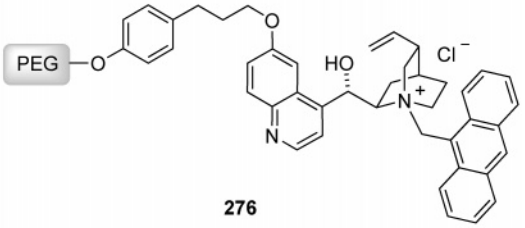
274

a; X = H **b**; X = O



275

a; X = H **b**; X = O



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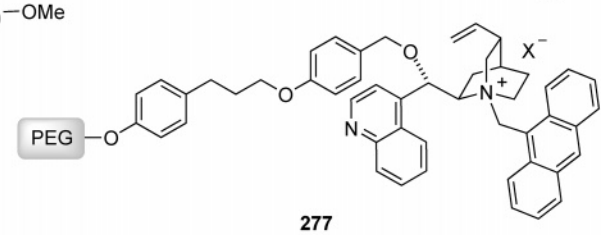

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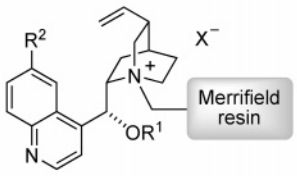
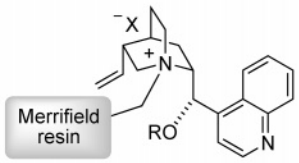


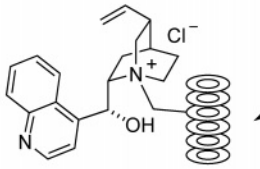
278

a; $R^1 = R^2 = H$, X = Cl
b; $R^1 = H$, $R^2 = O$-allyl, X = Br
c; $R^1 = Me$, $R^2 = H$, X = Cl



279

a; R = H, X = Cl
b; R = allyl, X = Br



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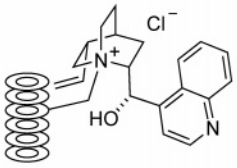

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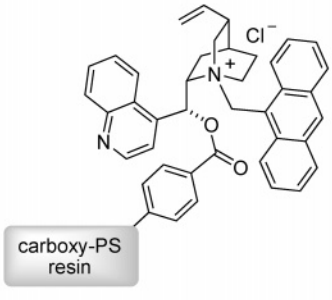
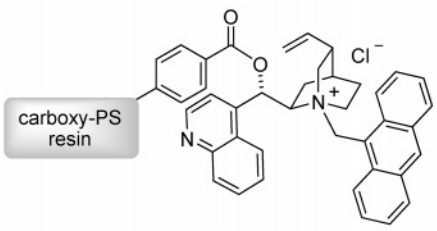


282



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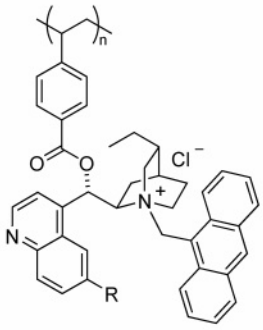
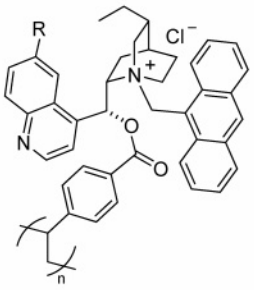


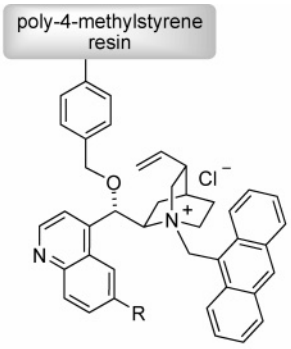
284

a; R = H **b**; R = OMe



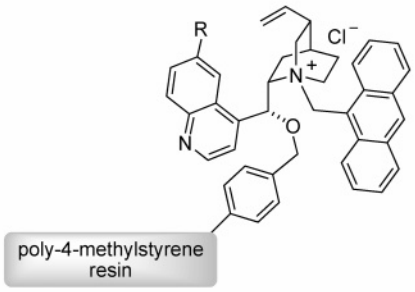
285

a; R = H **b**; R = OMe

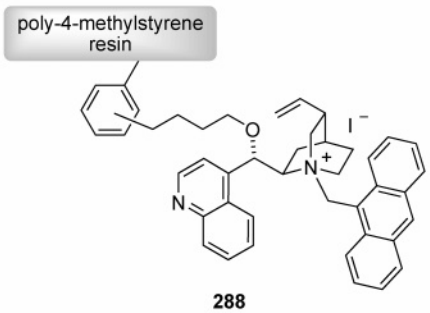


286

a; R = H **b**; R = OMe



287 **a**; R = H **b**; R = OMe



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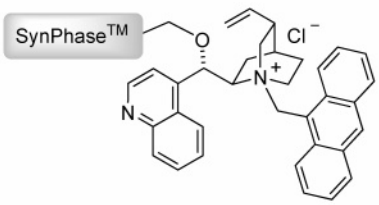

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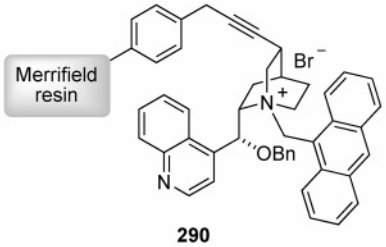

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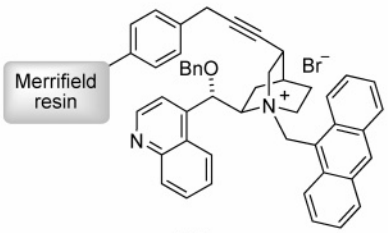

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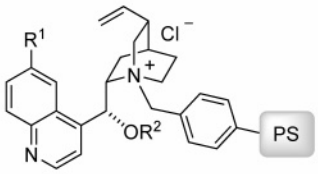
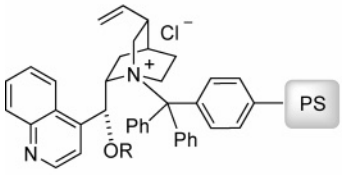
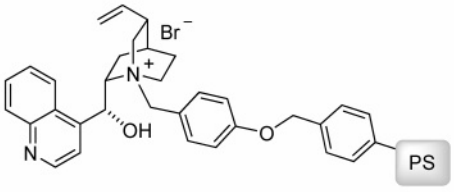


292 **a**; $R^1 = R^2 = H$
b; $R^1 = H$, R^2 = allyl
c; R^1 = OMe, $R^2 = H$



293

a; R = H **b**; R = allyl



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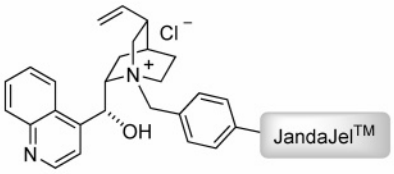

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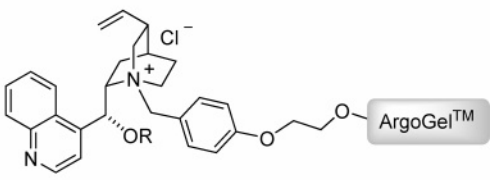


296

a; R = H **b**; R = allyl

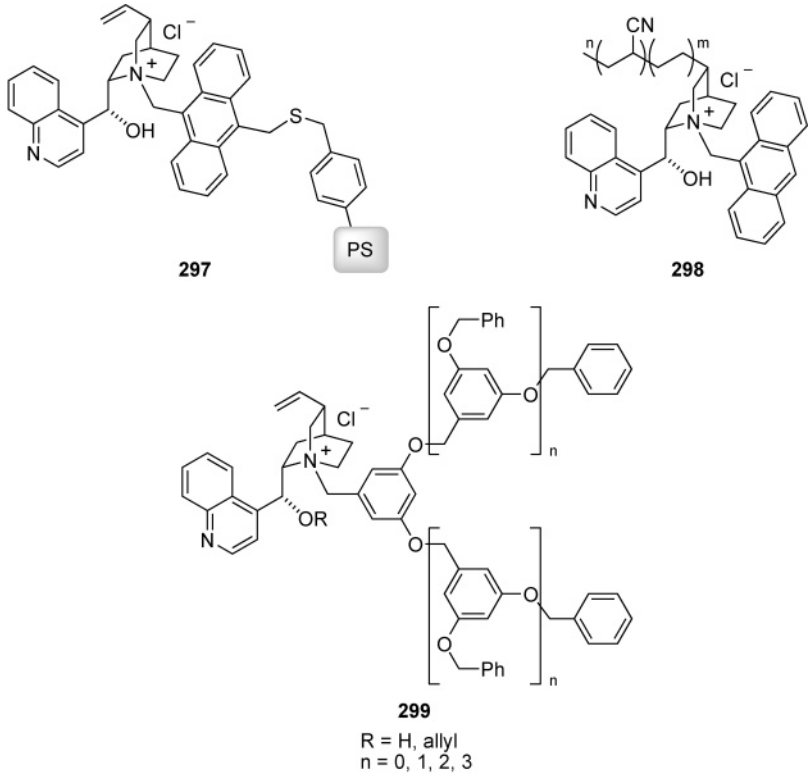
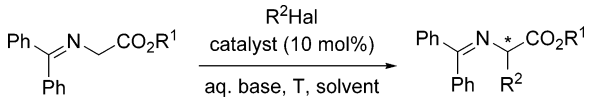


Figure 26. Polymer-supported PTC used in the enantioselective α-alkylation of **233**.

Table 17. Enantioselective Alkylation of α-Amino Esters 233 Using Polymer-Supported Ligands 271−299

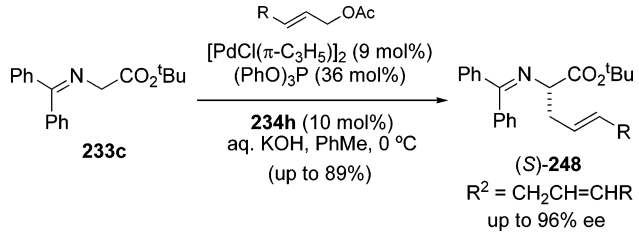


							product **248**			
entry	**233**	catalyst	R^5-Hal	base	solvent	*T* (°C)	yield (%)	config	ee (%)	ref
1	**233c**	**272b**	$PhCH_2$-Br	KOH	PhMe	20	83	(*S*)	73	261
2	**233c**	**272b**	cinnamyl-Br	KOH	PhMe	20	87	(*S*)	71	261
3	**233c**	**272a**	$PhCH_2$-Br	KOH	PhMe	0	84	(*S*)	81	262
4	**233c**	**274a**	$PhCH_2$-Br	KOH	PhMe	0	74	(*S*)	54	262
5	**233c**	**274b**	$PhCH_2$-Br	CsOH	PhMe	−60	72	(*S*)	71	262
6	**233c**	**277b**	$PhCH_2$-Br	CsOH	DCM	−78	75	(*S*)	64	263
7	**233c**	**278a**	$PhCH_2$-Br	NaOH	PhMe	0	90	(*S*)	90	264
8	**233c**	**278a**	$ArCH_2$-Br	NaOH	PhMe	0	up to 90	(*S*)	up to 90	264
9	**233c**	**278a**	allyl-Br	NaOH	PhMe	0	75	(*S*)	<35	264
10	**233c**	**272a**[a]	$PhCH_2$-Br	KOH	PhMe	0	84	(*S*)	81	265
11	**233c**	**284a**	$PhCH_2$-Br	CsOH	PhMe	−40	64	(*S*)	93	265
12	**233c**	**286a**	$PhCH_2$-Br	KOH	PhMe	0	70	(*R*)	63	265
13	**233c**	**291**	$PhCH_2$-Br	KOH	PhMe	0	72	(*R*)	63	265
14	**233d**	**292a**	$PhCH_2$-Br	NaOH	PhMe	0	90	(*S*)	90	266
15	**233d**	**299**	$ArCH_2$-Br	KOH	$PhMe/CHCl_3$	−60	up to 91	(*S*)	up to 72	267

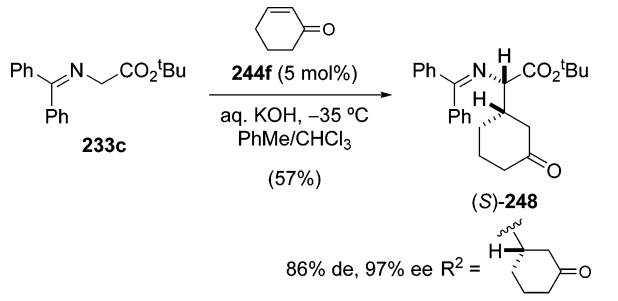
[a] Identical result was obtained when chiral catalyst **265a** was employed.

under the same conditions, that means, aqueous KOH in toluene at 0 °C; (c) chiral catalyst **273a** gave very good enantioselections (93% ee) of compound **248** (R^2 = Bn) at −40 °C using $CsOH·H_2O$ as base (Table 17, entry 11); (d) for the other series of cinchonine chiral recoverable catalysts, the most relevant examples were achieved (63% ee) with *O*-supported ligand **286a** and the ligand **291**, whose quinidine unit was bonded to the polymer at the vinylic moiety, under the same reaction conditions (Table 17, entries 12 and 13).[265] Another set of chiral supported catalysts **292**−**298** were synthesized and further utilized in the benzylation reaction of **233d**, being recovered by simple filtration. The best results (90% ee) were obtained when the catalyst **292a**, anchored to a Merrifield resin, was used at 0 °C with aqueous NaOH as base (Table 17, entry 14).[266] Dendritic cinchonidine ammonium salts **299** can be applied as PTC catalysts, but at this moment, the enantioselectivities are not so excellent to be extensively implemented. Only moderate ee's (up to 72% ee) were induced by the second generation of the polymeric ammonium salts **299** (R = H, *n* = 1) in the alkylation reaction of **233d** with benzyl bromides rather than alkyl iodides (Table 17, entry 15).[267] The dendrimers were

Scheme 31



Scheme 32



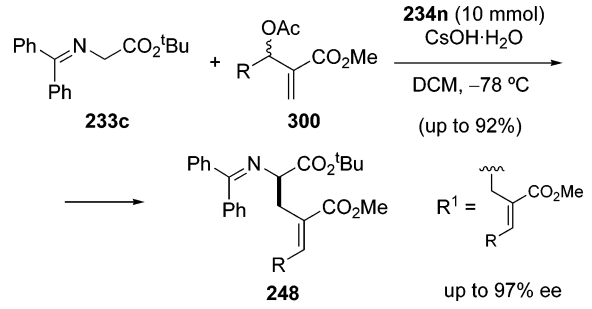
employed in the homogeneous phase using dialysis membrane bags.

The chiral PTC catalysts shown in Figures 22 and 26 can promote different reactions from the α-alkylations described previously. For example, the asymmetric allylation of the glycine imino ester **233c** through a chiral PTC using π-allyl palladium(II) complexes can generate two stereogenic centers on both the allylic substrate and the prochiral nucleophile. Catalyst **234h** (*O*-Me, *N*-anthracenylmethyl, 10 mol %) was effective in the palladium-catalyzed allylation of **233c**. The reaction was carried out using triphenylphosphite (36 mol %) and the palladium source (9 mol %) in aqueous KOH at 0 °C, providing high chemical yields and very good ee's (up to 96% ee) (Scheme 31).[268] The same reaction conditions were essayed with compound **233f** (R^1 = H, R^2 = Ar, R^3 = Me, R^4 = ^{t}Bu), but the chemical yield was very low (<24%), although with a good enantioselection (87% ee).[268]

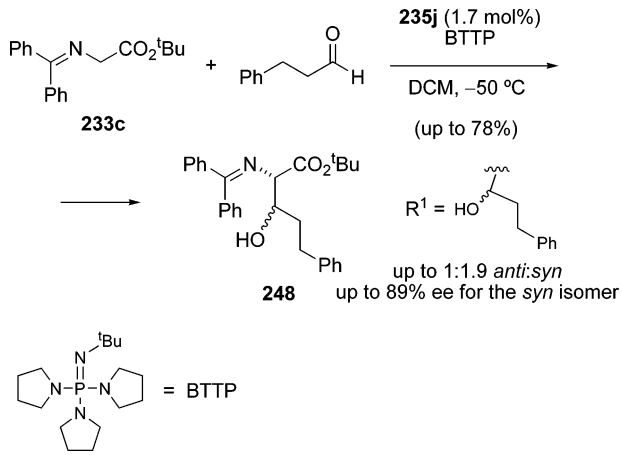
Much less studied conjugate additions of glycine enolates onto Michael acceptors can also be catalyzed by this type of ammonium salts. Following the pioneering work of Corey's group where high enantioselectivities were achieved by reaction of benzophenone imine *tert*-butyl glycinate **233c** onto different Michael acceptors employing CPTC agent **234n**,[269] dimeric cinchonidine and cinchonine-derived ammonium salts **244** have been used as PTC agents in the 1,4-addition of **233** to electron-deficient olefins. The enantioselectivity of the reaction (up to 97% ee) was dependent on the counteranion present in the chiral salt, with the catalysts being recovered by precipitation. The best enantioselectivity in open-chain acceptors was achieved for acrylonitrile using hexafluorophosphate-containing ammonium salts **244f**. The enantioselection was higher when cyclohexenone was used as conjugated alkene (Scheme 32).[270]

L-Lysine, L-ornitine, and L-proline were prepared (>95% ee) such that all site-directed ^{13}C and ^{15}N isotopomers can readily be obtained by the alkylation of the protected glycine derivative **233c** using Michael-type reactions with methyl acrylate and acrylonitrile in the presence of chiral cinchonidine-derived PTC agent **234n** (*O*-allyl, *N*-anthracenylmethyl) at room temperature.[271] Although the ee was not reported, it is presumed to be excellent, taking into account preceding works.[239]

Scheme 33



Scheme 34

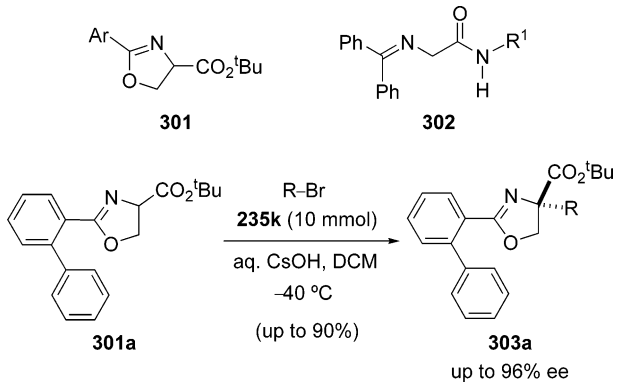


Following this particular reactivity, glutamic acid derivatives **248** were enantiomerically obtained (Scheme 33) by reaction of the enolate derived from **233c** with the electron-deficient olefin **300** (prepared by a Morita−Baylis−Hillman reaction), which possesses the appropriate functional groups in the right places for undergoing a sequential conjugate addition−β-elimination reaction. The cinchonidine-derived catalyst **234n** (*O*-allyl, *N*-anthracenylmethyl) was selected for this transformation run at −78 °C employing CsOH·H_2O as base in DCM (Scheme 33).[272] The best result (97% ee) was achieved when the electrophilic olefin **300** was bearing R = 4-NO_2-C_6H_4 as substituent.

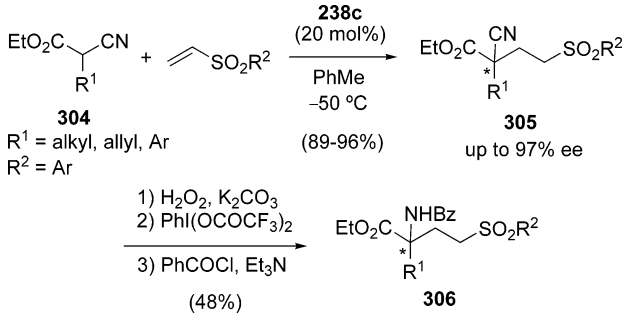
The extremely complex diastereo- and enantioselective catalyzed aldol reaction was also attempted by the inclusion of the new ammonium catalysts derived from dihydrocinchonidine **235**, with **235j** (R^1 = allyl, R^2 = 2,3,4-F_3-C_6H_2) being the most efficient for this process. The resulting β-hydroxy α-AAs **248** were isolated as *syn*-diastereoisomers in good ee. The Schwesinger BTTP base (1−2.5 equiv) accelerated the reaction at −50 °C, in DCM, and exhibited high levels of enantioselection favoring the *syn*-aldol product **248**, improving the results of this difficult transformation obtained in other previous contributions (Scheme 34).[273]

Other substrates, different from imino esters, such as serine-derived imidazolidines **301** or imine glycinamides **302** suffered the enantioselective alkylation catalyzed by chiral *Cinchona* derived salts. Thus, heterocycle **301a** gave the best enantioselection during its alkylation with benzyl bromide from a series of 2-aryloxazolines, and subsequently, the α-alkylation with different reactive allyl or benzylic bromides was studied. Dihydrocinchonidine-derived catalysts **235j**,**k** (10 mol %) (Figure 22) gave the best results (up to 96% ee) in DCM at −40 °C using CsOH as base. Finally, the hydrolysis of the heterocyclic ring **303a** furnished highly

Scheme 35



Scheme 36



enantiomerically enriched α-substituted serines (Scheme 35).[274]

Unfortunately, *N*-monosubstituted imine glycinamides **302** did not react as well as the corresponding ester does in all the tested conditions using **234a**, **c**, **j**, and **n** as chiral catalysts. The possible explanation for this low enantioselection can be attributed to a hydrogen bonding interaction between the NH (amide) and the nitrogen atom of the quinoline moiety.[275] Multiple *Cinchona* derivatives such as **192**−**194**, **224**−**226**, **238a**−**c**, and **239a**,**b** were used as chiral bases in the conjugate addition of α-substituted α-cyanoacetate **304** onto chiral sulfones, yielding α,α-disubstituted α-cyanoacetates **305**. The highest enantioselection (up to 97% ee) corresponded to the reactions involving a chiral base derived from quinine (*O*-anthracenylmethyl) **238c** (Figure 22) when the reaction was run at −25 °C. The conversions were very high, and finally the chiral α-AA derivatives **306** were obtained after a three-step sequence in a 43% overall yield (Scheme 36).[276]

4.1.1.2. Spiro Ammonium Salts Derived from Chiral Binol. The C_2-symmetric, spiro-type chiral quaternary ammonium bromides **307**−**319** (Figure 27) have been designed as pure synthetic chiral PTC agents and were prepared from commercially available (*R*)- or (*S*)-Binol as a source of chirality.[3c,e,f,l,o,232,233] If we compare the two families of chiral ammonium catalysts (this and the *Cinchona* derivatives), both induced very good to excellent enantioselectivities in the addition reactions of glycine or alanine derivatives onto electrophiles; however, spiranic catalysts can be successfully applied to a wider number of ketimine or aldimine Schiff bases. In general, it is easier to prepare a *Cinchona* derived catalyst than the spiro-type chiral quaternary ammonium salt, but this cannot be considered as a drawback but a valuable aspect because it allows modification of the structure of the chiral catalyst and modulate its enantiodiscrimination.[277] A dramatic effect of the steric hindrance, as well as the electronic properties of the aromatic substituents on the 3,3′ positions of the binaphthyl moiety, has been emphasized.[277]

One of the common features of the reactions performed using these catalysts (or the precedent chiral ammonium salts) is the employment of a mixture of toluene and aqueous basic solution (generally KOH) as solvent; however, lower amounts of the chiral spiranic ammonium salt than the *Cinchona*-derived catalysts are normally used. Chiral PTC biphenyl agent (*S*)-**307** was very effective in the α-alkylation reaction of the benzophenone *tert*-butyl glycinate **233c** using CsOH·H_2O or KOH as base, obtaining compounds **248** with high enantioselectivities (up to 99% ee) (Table 18, entries 1−4). This spiranic salt was employed as well in the short asymmetric synthesis of BIRT-377 (**208**) (see Scheme 24), a potent inhibitor of the interaction between intercellular adhesion molecules and antigens (Table 18, entry 5).[278] Instead of a chiral biphenyl unit, the chiral information can be provided by the chiral secondary amine, which reacts with the appropriate racemic bis(bromomethyl)biphenyl. Forty chiral **308** ammonium salts (Figure 27) were prepared and tested, obtaining the best enantioselections in the α-alkylation of substrate **233c** when (*R*)-*N*-methyl-1-naphthyl-1-ethylamine was used as chiral source. The enantioselectivities achieved were excellent when allylic and benzylic bromides were employed as electrophiles (Table 18, entries 6 and 7).[279] While unsubstituted (*R*,*R*)-**309a** induced very poor enantioselectivities, the chiral polysubstituted biphenyl framework (*R*,*R*)-**309b** exhibited an excellent enantiodiscrimination in the alkylation reactions of **233c** and **h** (up to 97% ee), except when using alkyl iodides, which caused a drop in the enantiomeric excesses (Table 18, entries 8−11).[280] Chiral binaphthyl PTC agents (*S*)-**310c**,**d** are powerful catalysts in the α-alkylation reactions of glycine and alanine imino esters **233c**,**h** for the asymmetric synthesis of α-alkyl and α,α-dialkyl α-AAs using a very low catalyst loading (Table 18, entries 12−15).[281] Not so good enantioselections were achieved either with chiral catalysts **311** or with (*S*,*S*)-**312a**−**e** in the alkylation of ketimines **233c**,**e**,**j** (Table 18, entries 16−18).[282] However, aldimine **233i** (derived from phenylglycine) was efficiently alkylated with allyl bromide by the intermediacy of the chiral PTC agent (*S*,*S*)-**312h** in the key step of the stereoselective synthesis of (2*S*,4*R*)-4-hydroxy-2-phenylproline (Table 18, entry 19).[283] It was also demonstrated that a dramatic rate enhancement occurred in the enantioselective α-alkylation of **233c** promoted by (*S*,*S*)-**312g** by combination of it with achiral crown ethers and derivatives. In this reaction, the ee of the final product **248** was not seriously altered if we compared the same result in absence of the racemic crown ether (Table 18, entries 20 and 21).[284] The aldimine Schiff bases bearing methyl and ethyl esters could be enantioselectively alkylated by alkyl iodides and allyl, benzyl, and propargyl bromides using chiral bis(binaphthyl) PTC agent (*S*,*S*)-**312h** (Table 18, entries 22−25). The lability of the terminal functional groups allowed a facile derivatization to other synthetically useful chiral building blocks.[285] Other substituted bis(binaphthyl) derivatives (*S*,*S*)-**312b**,**c** were the most suitable catalysts for the enantioselective α-alkylation of *tert*-butyl glycinate **233c**, giving, with chiral salt (*S*,*S*)-**313c**, slightly better enantioselections (Table 18, entries 26 and 27).[286] The design of the more complex bis(binaphthyl) ammonium salts (*S*,*S*)-**314e** and its direct application to the enantioselective alkylation of **233c** was described. This recyclable fluorous chiral compound could be recovered by extraction with perfluo-

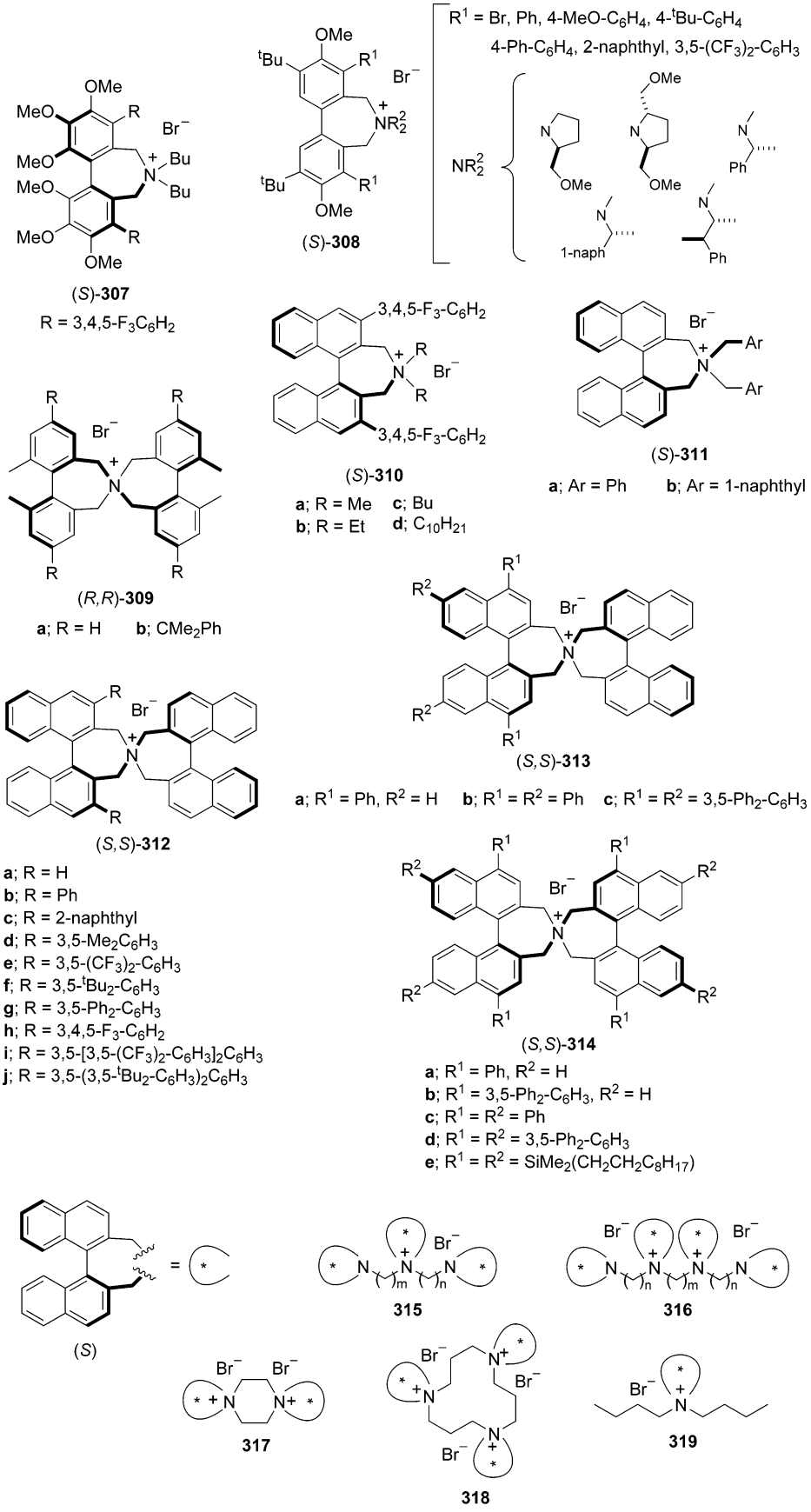
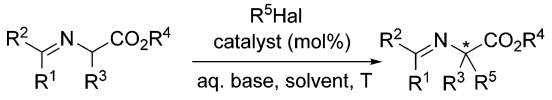


Figure 27. C_2-Symmetric spiro-type chiral quaternary ammonium bromides **307**−**319**.

rohexanes (FC-72) and reused in the synthesis of unnatural α-AAs with high enantioselectivities (up to 93% ee), as is recorded in Table 18 (entry 28).[287] Other (*S*,*S*)-**314** PTC series such as (*S*,*S*)-**314a**,**d** were evaluated, obtaining very similar results in terms of the enantioselectivity (up to 97% ee) in the reaction of the glycine derivative **233c** with several

Table 18. Enantioselective Alkylation of Compounds 233 Using Chiral Organocatalysts 307−319



233 **248**

c; $R^1 = R^2 = Ph$, $R^3 = H$, $R^4 = {}^tBu$
d; $R^1 = R^2 = Ph$, $R^3 = H$, $R^4 = Et$
e; $R^1 = R^2 = Ph$, $R^3 = H$, $R^4 = {}^iPr$
f; $R^1 = H$, $R^2 = 4\text{-}ClC_6H_5$, $R^3 = R^4 = Me$
g; $R^1 = H$, $R^2 = 4\text{-}ClC_6H_5$, $R^3 = Me$, $R^4 = Et$
h; $R^1 = H$, $R^2 = 4\text{-}ClC_6H_5$, $R^3 = Me$, $R^4 = {}^tBu$
i; $R^1 = H$, $R^2 = 4\text{-}ClC_6H_5$, $R^3 = Ph$, $R^4 = {}^tBu$
j; $R^1 = R^2 = Ph$, $R^3 = H$, $R^4 = Bn$

							product **248**			
entry	**233**	catalyst (mol %)	R^5-Hal	base	solvent	T (°C)	yield (%)	config	ee (%)	ref
1	**233c**	(*S*)-**307** (0.5)	RCH_2-Br[a]	KOH	PhMe	0	up to 99	(*R*)	up to 96	278
2	**233c**	(*S*)-**307** (1−0.05)	$ArCH_2$-Br	KOH	PhMe	25	up to 97	(*R*)	up to 98	278
3	**233c**	(*S*)-**307** (0.1)	Et-I	KOH	PhMe	25	up to 80	(*R*)	up to 94	278
4	**233h**	(*S*)-**307** (1)	$PhCH_2$-Br	CsOH	PhMe	0	73	(*R*)	99	278
5	**233h**	(*S*)-**307** (1)	$4\text{-}BrC_6H_4CH_2$-Br	CsOH	PhMe	0	83	(*R*)	97	278
6	**233c**	**308** (1)	RCH_2-Br[a]	KOH	PhMe	30	up to 99	(*R*)	up to 96	279
7	**233c**	**308** (1)	$ArCH_2$-Br	KOH	PhMe	30	up to 97	(*R*)	up to 97	279
8	**233c**	(*R*,*R*)-**309b** (1)	RCH_2-Br[a]	KOH	PhMe	−20	up to 99	(*S*)	up to 97	280
9	**233c**	(*R*,*R*)-**309b** (1)	$ArCH_2$-Br	KOH	PhMe	−20	up to 97	(*S*)	up to 97	280
10	**233c**	(*R*,*R*)-**309b** (1)	allyl-I	KOH	PhMe	−20	up to 88	(*S*)	up to 86	280
11	**233h**	(*R*,*R*)-**309b** (1)	$PhCH_2$-Br	KOH	PhMe	−20	82	(*S*)	95	280
12	**233c**	(*S*)-**310c**,**d** (0.05)	RCH_2-Br[a]	KOH	PhMe	0	up to 88	(*R*)	up to 98	281
13	**233c**	(*S*)-**310c**,**d** (0.05)	$ArCH_2$-Br	KOH	PhMe	0	up to 98	(*R*)	up to 99	281
14	**233c**	(*S*)-**310c**,**d** (0.05)	Et-I	KOH	PhMe	−20	67	(*R*)	99	281
15	**233h**	(*S*)-**310c** (0.05)	$PhCH_2$-Br	KOH	PhMe	−20	63	(*R*)	98	281
16	**233c**	(*S*,*S*)-**312c** (1)	$PhCH_2$-Br	KOH	PhMe	0	up to 96	(*R*)	up to 96	282
17	**233e**	(*S*,*S*)-**312a** (1)	$PhCH_2$-Br	NaOH	PhH	0	up to 80	(*R*)	up to 45	282
18	**233i**	(*S*,*S*)-**312a** (1)	$PhCH_2$-Br	NaOH	PhH	0	up to 94	(*R*)	up to 40	282
19	**233i**	(*S*,*S*)-**312h** (0.5)	allyl-Br	KOH	PhMe	0	81	(*S*)	91	283
20	**233c**	(*S*,*S*)-**312g** (0.05)	allyl-Br	KOH	PhMe	0	up to 93	(*S*)	up to 91	284
21	**233c**	(*S*,*S*)-**312g** (0.05)	$ArCH_2$-Br	KOH	PhMe	0	up to 97	(*S*)	up to 98	284
22	**233d**	(*S*,*S*)-**312h** (1)	RCH_2-Br[a]	KOH	PhMe	0	up to 81	(*R*)	up to 96	285
23	**233d**	(*S*,*S*)-**312h** (1)	$ArCH_2$-Br	KOH	PhMe	0	up to 99	(*R*)	up to 98	285
24	**233d**	(*S*,*S*)-**312h** (1)	Et-I	KOH	PhMe	0	75	(*R*)	93	285
25	**233g**	(*S*,*S*)-**312h** (1)	$ArCH_2$-Br	KOH	PhMe	−20	up to 89	(*R*)	up to 98	285
26	**233c**	(*S*,*S*)-**313b**,**c** (1)	RCH_2-Br[a]	KOH	PhMe	0	up to 92	(*R*)	up to 88	286
27	**233c**	(*S*,*S*)-**313b**,**c** (1)	$ArCH_2$-Br	KOH	PhMe	0	up to 93	(*R*)	up to 96	286
28	**233c**	(*S*,*S*)-**314e** (3)	$ArCH_2$-Br	KOH	PhMe	0	up to 93	(*S*)	up to 93	287
29	**233c**	(*S*,*S*)-**314a-d** (1)	RCH_2-Br[a]	KOH	PhMe	0	up to 92	(*R*)	up to 95	288
30	**233c**	(*S*,*S*)-**314a-d** (1)	$ArCH_2$-Br	KOH	PhMe	0	up to 91	(*R*)	up to 97	288
31	**233c**	**316** (3)	$PhCH_2$-Br	KOH	PhMe	0	78	(*S*)	97	289

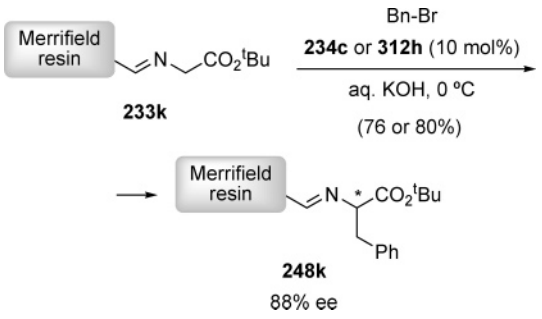
[a] Allyl and propargyl bromides.

activated halogenides (Table 18, entries 29 and 30).[288] The new set of polyamine-based chiral PTC systems **315**−**319** was studied in the synthesis of the enantiomerically enriched phenylalanines. The combination of (*S*)-**316** ($m = 4$, $n = 3$), benzyl bromide, and imino ester **233c** gave rise to the desired product with the highest ee (83%) in good chemical yields (Table 18, entry 31).[289]

The Schiff base anchored to a Merrifield resin **233k** could be enantioselectively alkylated by the employment of *Cinchona*-derived or spiranic ammonium salts as catalysts. Under the same reaction conditions, chiral PTC agents **234c** and **312h** operated with the same efficiency and chemical yield, furnishing the supported α-AA derivatives with opposite absolute configuration (Scheme 37).[290] Other alkylations were performed with **234c** using $CsOH{\cdot}H_2O$ as base at −20 °C; thus, alkyl, allyl, propargyl, and benzylic bromides afforded supported compounds **248** with ee's ranging from 86 to >99%.[290]

As occurred in the reactions involving *Cinchona*-derived catalysts (Scheme 35), *tert*-butoxycarbonyloxazoline **301b** was an appropriate substrate in the enantioselective alkylation reactions promoted by chiral PTC agent (*S*,*S*)-**312h** (2.5 mol %) in toluene at 0 °C, and using KOH as base. The

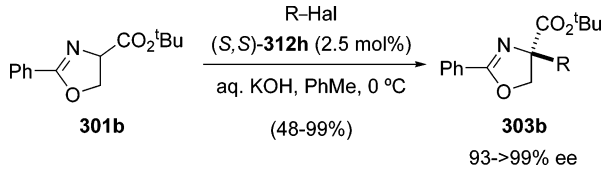
Scheme 37



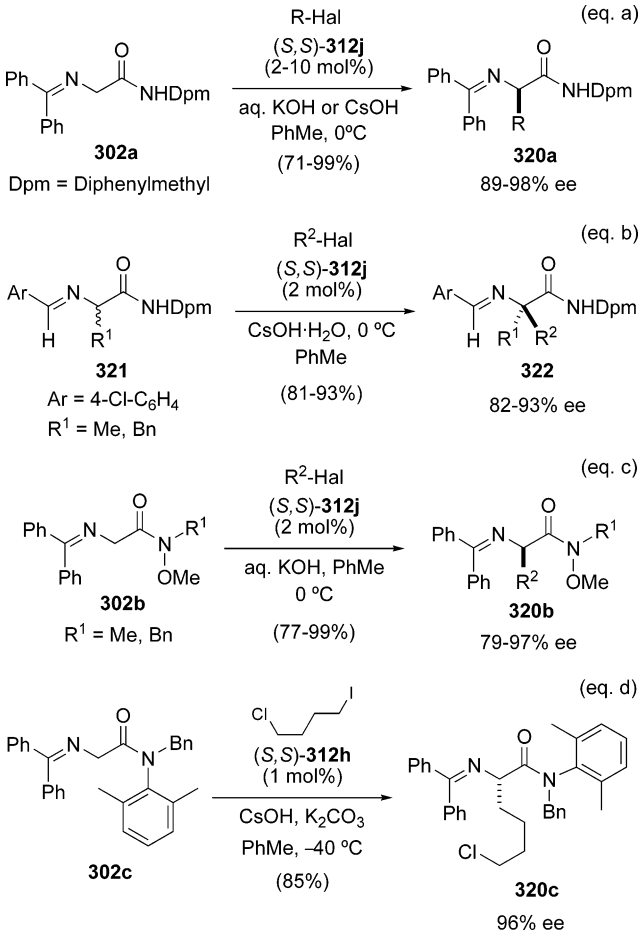
enantiomeric ratios were very high, obtaining in many cases ee > 99% of the corresponding heterocycle **303b**, especially for the examples performed with benzylic bromides (Scheme 38).[291] This methodology constituted a straightforward approach to enantiomerically enriched α-alkylated serines after hydrolysis of the oxazoline ring.

Imine amides **302a**, **321**, and **320b** proved to be valuable substrates for this type of enantioselective catalysis performed by spiro ammonium salts, unlike the reaction carried out with *Cinchona* derived catalysts.[292−295] They were allowed to react with different halogenides, obtaining compounds **320a**, **322**,

Scheme 38

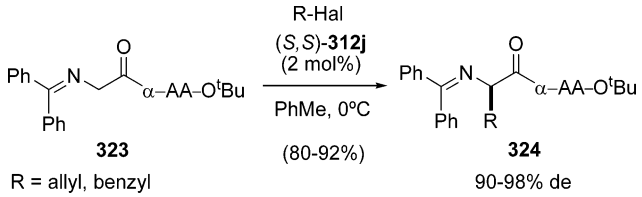


Scheme 39

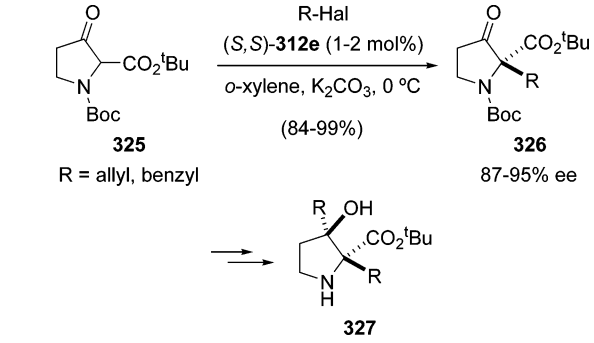


and **320b**, respectively (Scheme 39, eqs a−c). The reaction conditions were very similar between them, and the common catalyst (*S*,*S*)-**312j** was added in a 10 mol % proportion when hindered iodides were used as electrophiles.[292,293] Compound **302a** reacted with benzylic bromides, iodoalkanes, iodocycloalkanes, and isopropyl iodide in very good chemical yield (Scheme 39, eq a).[292,293] Amide **321** seems to be slightly less reactive, although cyclopentyl iodide and 1-iodobutane gave very high chemical yields (Scheme 39, eq b).[292] The Weinreb-type glycine amide **302b** reacted with benzylic bromides and iodoalkanes but not with secondary iodides (Scheme 39, eq c).[292] The resulting amides **320a**, **322**, and **320b** are very interesting chiral building blocks because an enormous number of transformations of the amido group can be successfully promoted, generating vicinal diamines, α-amino ketones, and *β*-amino alcohols.[292,293] An example of these applications was the enantioselective alkylation of the amide **302c** with 1-chloro-4-iodobutane catalyzed by (*S*,*S*)-**312h**. The resulting optically enriched amide **320c** (obtained in 96% ee) constituted the key intermediate in the synthesis of levobupivacaine, an anaesthetic agent for postoperative pain management (Scheme 39, eq d).[294] In this context, highly stereoselective *N*-terminal functionalization

Scheme 40



Scheme 41



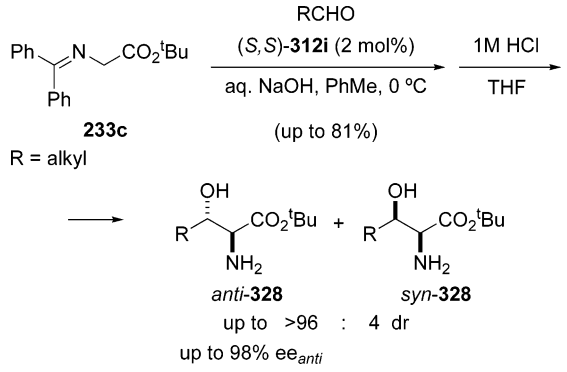
of small peptides can be done in the presence of chiral PTC catalysts. Although the reaction is diastereoselective (up to 98% de), it is convenient to remark that the ketimine of the dipeptide Gly-L-Phe-O^{t}Bu, as well as the other five compounds Gly-L-α-AA-O^{t}Bu, **323** (AA = Leu, Val, Tyr, Ala, Pro), were alkylated using chiral PTC agent (*S*,*S*)-**312j** (2 mol %), obtaining dipeptides **324**, which demonstrated the matched combination between the two chiral arrangements (Scheme 40). In this work, dipeptides and tripeptides were allowed to undergo the same transformation, obtaining the analogous alkylated tripeptides and tetrapeptides in very high yield and de up to 98%.[295]

The 3-oxoproline derivative **325** was selected as substrate for the synthesis of aza-cyclic-α-AA derivatives **326** with a quaternary stereocenter. This process has been accomplished by the chiral PTC alkylation using a bis(binaphthyl) spiro ammonium salt (*S*,*S*)-**312e** with benzylic and allylic bromides as electrophiles. The ee's of the products **326** were very high, and immediately they were transformed into the novel cyclic α-AA derivatives **327** by taking advantage of the presence of the 3-keto functional group (Scheme 41).[296]

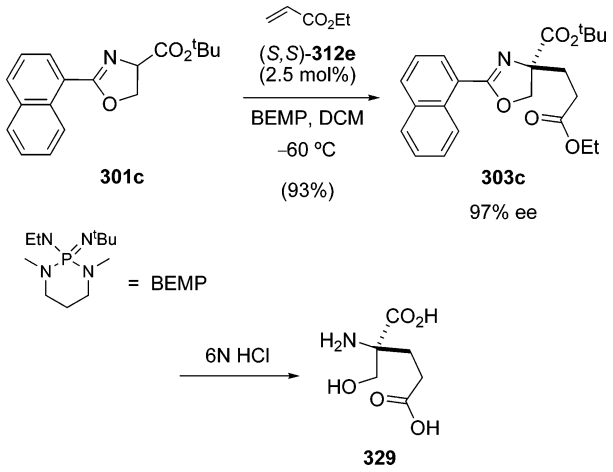
Imino ester **233c** underwent an aldol reaction catalyzed by spiro compound (*S*,*S*)-**312i**. The best *anti*/*syn* ratio corresponded to the addition of the enolate onto the α-(triisopropylsilyloxy)acetaldehyde, affording cleanly the derived *β*-hydroxy-α-amino ester *anti*-**328** with very high stereochemical control (>96/4 *anti*/*syn* ratio and 98% ee for the *anti*-isomer). Dihydrocinnamaldehyde and heptanal also gave very good *anti*/*syn* ratios in good chemical yields and enantioselectivities (Scheme 42).[297] The stereochemical outcome of these reactions contrasts significantly with the major *syn*-diastereoselectivity observed when a chiral PTC agent derived from cinchonidine **235j** was used (see Scheme 34).

The 1,4-conjugate addition of 2-aryl-2-oxazoline-4-carboxylate **301c** was optimized by modifying all of the possible parameters, finding that the best base was the Schwesinger nonionic neutral phosphazene base dimethylperhydro-1,3,2-diazaphosphorine (BEMP), operating at −60 °C. In this case, the yield was very high (93%) and the chiral induction was very noticeable (97% ee). This example represented the first catalytic method for the enantioselective synthesis of (2*S*)-α-(hydroxymethyl)glutamic acid **329** (Scheme 43).[298]

Scheme 42



Scheme 43



4.1.1.3. Other Ammonium Salts. With the objective of emulating the effectiveness of the last two extensive families of chiral PTC agents, many ammonium salts have been prepared and tested as organocatalysts in these types of chemical transformations, with some of them giving very high enantiomeric ratios. The most relevant of these salts appearing in the literature during the last 3 years are collected in Figure 28.

As is described in Table 19, these chiral catalysts **330**−**338** are not widely used in many transformations due to the variable enantioselectivity depending on the electrophile employed. Catalysts derived from tartaric acid **332**,[302,303] **334**,[305] and **335**[306] offered a very low or null enantioselection. However, (*S*,*S*)-Tadias **330c** exhibited very good enantioselections in either enantioselective α-alkylation or Michael-type addition reaction of substrates **233** in very good yields and very high ee (up to 94% ee). The alkylation with allylic, propargylic, and benzylic bromides proceeded with higher stereocontrol at −70 °C and using CsOH as base, while Michael-type addition reactions were performed at higher temperature, −30 °C, and also employing CsOH as base (Table 19, entries 1−4).[299,300] Moreover, dramatic counteranion effects were observed in PTC for the first time, making it possible to further improve reactivity and selectivity. These findings validated the usefulness of three-dimensional fine-tuning of the catalysts for optimization. PTC agent **330c** was successfully used in the enantioselective synthesis of the precursor of the serine protease inhibitor aeruginosin 298-A and its analogues (Table 19, entry 4).[299,300]

The ammonium salts **330** were also useful in the enantio- and diastereoselective catalytic Mannich-type reaction of the imino ester **233c** with *N*-Boc-imines. Tadias ligands are, in general, very stable under strongly basic conditions, and it can be recovered after recrystallization from the reaction mixture in high yield (approximately 90%). The two-center PTC **330e**−**k** induced a moderate to high enantioselection (up to 82% ee) of the *anti*-α,*β*-diamino acid derivatives, which are relevant compounds for pharmaceutical purposes (Table 19, entry 5).[301]

Catalyst (*S*)-**333a**, derived from (*S*)-Binol, was the most efficient of this series, obtaining compounds **248** with moderate ee's (up to 75%) *via* Michael-type addition reaction onto electron-deficient alkenes (such as acrylic esters, acrylonitriles, acrylamides, and vinyl sulfones) using Cs_2CO_3 as base and chlorobenzene as solvent at −30 °C (Table 19, entry 6).[304]

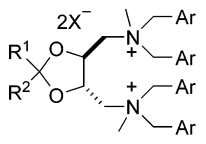
The development of an elevated number of chiral ammonium salts **336a**−**o**, derived from the corresponding chiral epoxides, was not fruitful because only a 58% ee was achieved, as a better result, during the enantioselective benzylation of **233c** catalyzed by **336o** (1 mol %) at 0 °C (Table 19, entry 7).[307] An identical situation occurred with ephedrine-derived ammonium salts **337a**−**g**, but on this occasion, the best result (95% ee) was originated when the α-benzylation reaction of **233c** was carried out with *O*-2-naphthylmethylephedrine-derived catalysts **340c** (Table 19, entry 8).[308] The L-menthol structure was properly modified in order to obtain chiral organocatalyst **338**, which gave, in general, low to moderate enantioselections. The best result, in terms of the enantioselectivity, was identified in the alkylation of the Schiff base **233c** with 1-iodohexane, catalyzed by **338e** (10 mol %) (Table 19, entry 9).[309]

4.1.2. Chiral Metal Complex-Promoted Electrophilic Additions

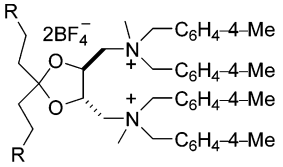
The employment of chiral ligand−metal complexes derived from enolates for the asymmetric synthesis of α-AA will be described in this section. Particularly, amino alcohols with axial chirality,[310] chiral crown ethers,[311] chiral metal−salen complexes,[4,312] and chiral palladium complexes[313] are the most suitable alternatives for the enantioselective alkylation or allylation, respectively, of the glycine and α-monosubstituted glycine derivatives. These alternatives, developed during the last 15 years, have, even today, experienced significant progress. Apart from the references included in the very recent reviews concerning the reactivity of chiral metal−salen complexes,[312] some interesting contributions from the last 2 years have to be considered.

Initially, organocatalyst Nobin (*R*)-**339a** was a profitable ligand or cocatalyst in many transformations: one of them was the catalytic enantioselective α-alkylation/1,4-addition reaction of the ketimine nickel(II) complex **340**. The enantioselective Nobin-mediated benzoylation of the nickel complex **340** took place at room temperature in DCM, employing the inexpensive NaOH as base and a 10 mol % charge of catalyst. Compound (*S*)-**341** was obtained in 86% yield and very good enantioselectivity (97% ee, Scheme 44, eq a).[310] For the 1,4-Michael-type addition reaction of **340** with methyl acrylate, sodium hydride was used as base. At room temperature, and using a smaller amount of the catalyst **339a** (2.4 mol %), the product (*S*)-**341** was achieved in 88% yield and 94% ee (Scheme 44, eq a).[310]

The crown ether **342**, derived from the *chiro*-inositol L-quebrachitol, was successfully employed as a catalyst (0.2 mol %) in the 1,4-addition reaction of the glycine template **233c** onto acrylates and methyl vinyl ketone (MVK),

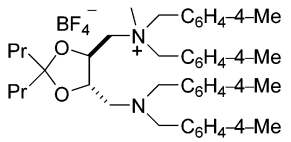


(*S,S*)-**330** (Tadias)

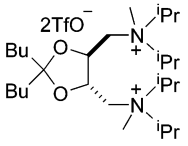


(*S,S*)-**330** (Tadias)

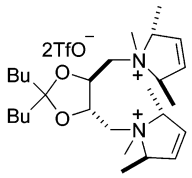
a; $R^1 = R^2$ = Pr, Ar = 4-Me-C_6H_4, X = BF_4
b; $R^1 = R^2$ = Pr, Ar = 4-Me-C_6H_4, X = Br
c; R^1 = ^{t}Bu, R^2 = Me, Ar = 4-Me-C_6H_4, X = Br
d; R^1 = ^{t}Bu, R^2 = Me, Ar = 4-Me-C_6H_4, X = BF_4
e; R = H **h**; R = Bn
f; R = Me **i**; R = 4-^{t}Bu-C_6H_4 **k**; R = 4-F-C_6H_4
g; R = Ph **j**; R = 2,4,6-Me_3-C_6H_2



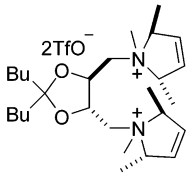
(*S,S*)-**331**



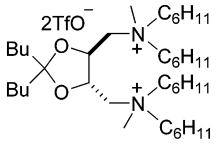
(*S,S*)-**332a**



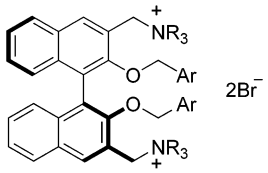
(*S,S*)-**332b**



(*S,S*)-**332c**

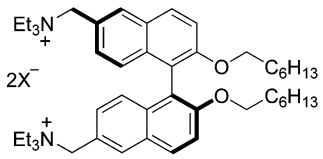


(*S,S*)-**332d**



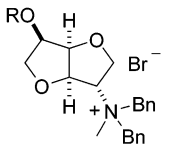
(*S*)-**333**

a; Ar = 4-(CF_3)-C_6H_4, NR_3 = NEt_3
b; Ar = Ph, NR_3 = NEt_3
c; Ar = 4-MeO-C_6H_4, NR^3 = NEt_3
d; 4-(CF_3)-C_6H_4, NR_3 = $BnNEt_2$
e; 4-(CF_3)-C_6H_4, NR_3 =

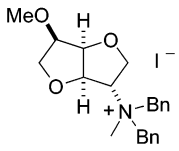


(*S*)-**334**

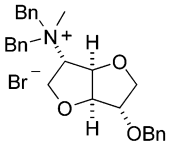
a; X = I **b**; X = OTs **c**; 2X = HPO_4^{2-}/PO_4^{3-}



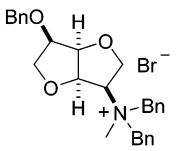
335



335d

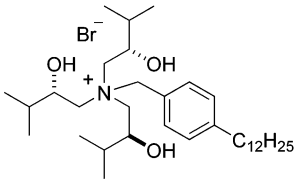


335e

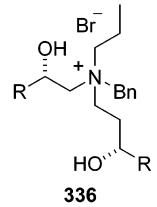


335f

a; R = Me
b; R = allyl
c; R = Bn

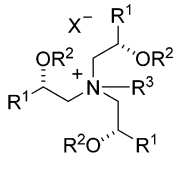


336a



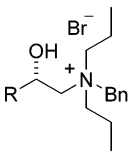
336

b; R = CH_2OPh
c; R = ^{i}Pr



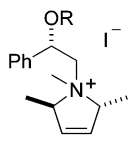
336

f; R^1 = CH_2OPh, R^2 = H, R^3 = Bn, X = Br
g; R^1 = CH_2OPh, R^2 = allyl, R^3 = Bn, X = Br
h; R^1 = $CH_2O(CH_2)_{10}Me$, R^2 = H, R^3 = Bn, X = Br
i; R^1 = Ph, R^2 = H, R^3 = Bn, X = Br
j; R^1 = Cy, R^2 = H, R^3 = Bn, X = Br
k; R^1 = ^{i}Pr, R^2 = Bn, R^3 = Bn, X = Br
l; R^1 = ^{i}Pr, R^2 = H, R^3 = 3,5-$(MeO)_2C_6H_3CH_2$, X = Br
m; R^1 = ^{i}Pr, R^2 = H, R^3 = 4-$BrC_6H_4CH_2$, X = Br
n; R^1 = ^{i}Pr, R^2 = H, R^3 = ($H_{25}C_{12}$)-$C_6H_4CH_2$, X = Br
o; R^1 = ^{i}Pr, R^2 = H, R^3 = Bn, X = TfO



336

d; R = CH_2OPh
e; R = ^{i}Pr



337

a; R = H **b**; R = Bn
c; R = 2-naphthylmethyl
d; R = 9-anthracenylmethyl

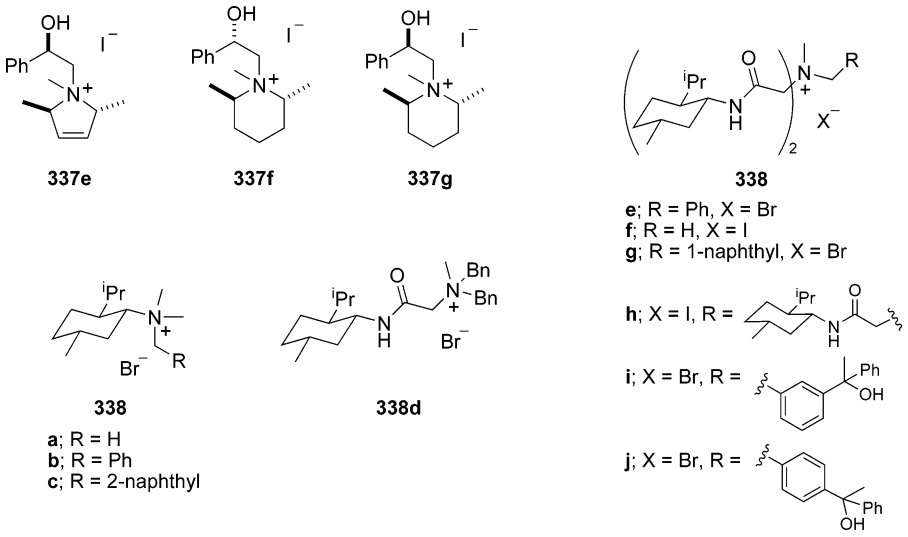
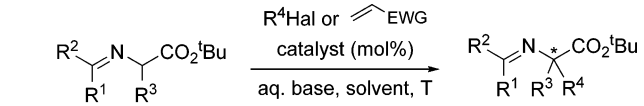


Figure 28. Several chiral phase transfer catalysts, **330**−**338**, used for the enantioselective α-alkylation.

Table 19. Enantioselective Alkylation Reactions of Compounds 233 and 344 Using Chiral Organocatalysts 333−343



							product **248**			
entry	**233**	catalyst (mol %)	electrophile	base	solvent	*T* (°C)	yield (%)	config	ee (%)	ref
1	**233c**	(*S*,*S*)-**330c** (10)	RCH_2-Br[a]	CsOH	PhMe/DCM	−70	73−93	(*R*)	up to 91	299, 300
2	**233c**	(*S*,*S*)-**330c** (10)	$ArCH_2$-Br	CsOH	PhMe/DCM	−70	71−93	(*R*)	up to 94	299
3	**233h**	(*S*,*S*)-**330c** (10)	benzyl/allyl-Br	KOH	PhMe/DCM	4	80−87	(*R*)	up to 74	299
4	**233c**	(*S*,*S*)-**330c** (10)	ethyl acrylate	Cs_2CO_3	PhCl	−30	71	(*S*)	82	299
5	**233c**	(*S*,*S*)-**330e**−**k** (10)	*N*-Boc-imines	Cs_2CO_3	PhF	−20/−40	95−99	(*S*)	up to 82[b]	301
6	**233c**	(*S*)-**333a** (1)	CH_2=CH-EWG	Cs_2CO_3	PhCl	−30	up to 100	(*S*)	up to 75	304
7	**233c**	**336o** (1)	Bn-Br	KOH	PhMe	0	55	(*S*)	58	307
8	**233c**	**337c** (0.5−5)	$ArCH_2$-Br	CsOH	PhMe	0	up to 83	(*R*)	up to 95	308
9	**233c**	**338e** (10)	R-Hal	KOH	PhMe/DCM	−20	up to 92	(*R*)	up to 72	309

[a] Allyl and propargyl bromides. [b] For the major *syn*-diastereoisomer.

obtaining very good enantioselectivities at very low temperatures. For example, the reaction with methyl acrylate led to the corresponding Michael adduct (*S*)-**248** in very high yield and excellent enantioselectivity (Scheme 44, eq b).[311]

Very interesting aspects about the mechanism of the reactions promoted by metal−salen complexes and the evaluation of every parameter that governs the reaction course were clarified.[314,315] The influence of the metal ion and chiral diamine, used to form the metal−salen complex, in the asymmetric benzylation of an alanine-derived enolate was investigated. Curiously, metal ions, which can form square-planar complexes, gave catalytically active species, and the best results were obtained with metal ions from the first row of the transition metals, particularly copper(II) and cobalt(II), **343b** and **343e**, respectively (Figure 29). An example of this efficiency is shown in Scheme 45 (eq a), where the alaninate **233l** was benzylated in high yield and notable enantioselection. From the data of this reaction and other results, it was suggested that the mechanism may involve a single electron-transfer process. Also, salen ligands derived from acyclic chiral 1,2-diamines were found to generate poor enantioselections in the corresponding alkylation reactions. Complexes derived from a variety of five- and six-membered cyclic 1,2-diamines gave active catalysts, but the enantioselectivity was always far lower than that for the parent cyclohexane-1,2-diamine derived complexes **343**.[314a] A study of the effect of the substituents in the imino ester (aromatic positions and at the α-position) was performed, obtaining the best result when using compound **233m** (R^1 = Et, X = Cl) and benzyl bromide. In this example, compound **248m** was isolated with a 82% ee (Scheme 45, eq b).[314b,c] A transition state model was reported, which accounts for the influence of the size of the side chain on the final enantioselectivity. Another parameter surveyed in these type of processes was the influence of the aromatic substituents on the salen ligand−metal(II) complex. Glycine Schiff base **233m** (R^1 = Me, X = Cl) was benzylated in the presence of salen ligands **344a**−**h**−copper complexes, discovering that a strong influence of the substituents in the aromatic rings of the salen ligand exists. In fact, better enantioselection was achieved with chiral copper complex **343b** than with the chiral copper complex **344e**.[315a] The same authors published mechanistic studies on this asymmetric alkylation of esters **233** using a salen ligand **343b**−copper-(II) complex as catalyst. A reaction with a buildup of positive charge in the transition state would be expected to favor the

more electron-rich benzylic bromides, but the fast reactions with electron-deficient benzylic bromides rule out any possibility of the transition state possessing a significant amount of positive charge. According to the Hammet plot, the U-shaped curve predicted an asynchronous S_N2 reaction involving a negatively charged nucleophile. It is also probable that part of the role of the catalyst **343b** is to enhance the nucleophilicity of the enolate. The degree of asynchronicity can be connected with the faster cleavage of the carbon−halogen bond than the formation of the carbon−enolate bond. These and other experimental details explained why only alkylating agents (reactive under S_N2 conditions) reacted so well with the enolates.[315b]

The quaternary stereogenic center at the α-position of the α-AAs leads to many desirable properties associated with this class of α-AA, and a few processes are able to construct the mentioned quaternary optically enriched structures. Although chiral PTC agents achieve this arrangement (see above), the enantioselective allylic alkylation, promoted by chiral palladium complexes, is the most employed methodology to achieve this goal.

Glycine or α-substituted glycine Schiff bases **233a**−**n** have been evaluated in the palladium-catalyzed asymmetric allylation reactions with chiral ligands **345**−**360**, (*S*)-**87a** (Binap), and the cinchonidinium ammonium salt **234h** (Figure 30), with the ferrocenylphosphine (*R*,*R*)-**347a** being the most efficient ligand. From all of the glycine and α-substituted glycine derivatives essayed, *tert*-butyl alaninate **233n** provided the best enantioselection of the final product **248n** (Scheme 46).[316]

The reaction of the enolates derived from **233** with unsymmetrical allylation agents, catalyzed by chiral palladium complexes, is a tough and challenging task, because regio-, diastereo-, and enantioselectivity must be controlled. It is well-known that allylic acetates reacted by their less hindered position with nucleophiles **233** using *Cinchona* alkaloid derived catalyst (see Scheme 31).[268] In contrast to the palladium catalysis, some transition metals, such as iridium,[313a] molybdenum,[313d] and tungsten,[313d] promoted the allylic alkylation at the more highly substituted terminus of the allylic substrates. The iridium-catalyzed allylic substitution with allylic phosphates and glycine Schiff base **233c** was investigated. The optimal reaction conditions are described in Scheme 47, obtaining different *anti*/*syn* product ratios depending on the base employed. With KOH (Scheme 47, eq a) the *syn*-stereoisomer **248o** was the major product, obtained in excellent enantioselective excess; however, the *anti*/*syn* ratio was opposite if LiHMDS was used as base, achieving very high enantioselections of both stereoisomers (Scheme 47, eq b).[317]

Azalactones **361**, derived from different amino acids, are easily accessible compounds with a highly acidic α-hydrogen. After finishing the desired chemical transformation, α-AA or α-AA-derivatives can be obtained by hydrolysis of the heterocycle under mild acidic conditions. These systems are ready to be used as activated carbonucleophiles in the palladium-catalyzed allylation reaction.[313b,d] The unsymmetrical 3-acetoxycyclohexene allowed the simultaneous generation of a second stereogenic center in the final product **362a**. The highest diastereomeric and enantiomeric excesses were obtained for the valine derivative **361c** in the reaction catalyzed by (*R*,*R*)-**346** (Scheme 48, eq a).[318] In addition, a large series of unsymmetrical allylic acetates have been tested, with all of them exhibiting excellent enantioselections when the catalyst was (*R*,*R*)-**346** rather than (*R*,*R*)-**347a**, (*S*,*S*)-**348**, (*R*,*R*)-**349**, and **351** (Scheme 48, eq b). The preference of the nuceophile for the less hindered position of the allylic system was also demonstrated once more, with no detection of any significant amount of the regioisomer originated by the attack at the less accessible allylic position.[318] This last transformation, using a more complex allylic acetate, served as a key step for the total synthesis of sphingofungins E and F.[319]

An example of the molybdenum-catalyzed reaction including a reversal regiochemistry, which means the major product was originated by the typical attack onto the most hindered allylic position, could be observed in Scheme 49, in which the azlactone **361b**, generated in the presence of ligand (*S*,*S*)-**350** and molybdenum, furnished the product **362c** with excellent diastereo- and enantioselectivity.[320]

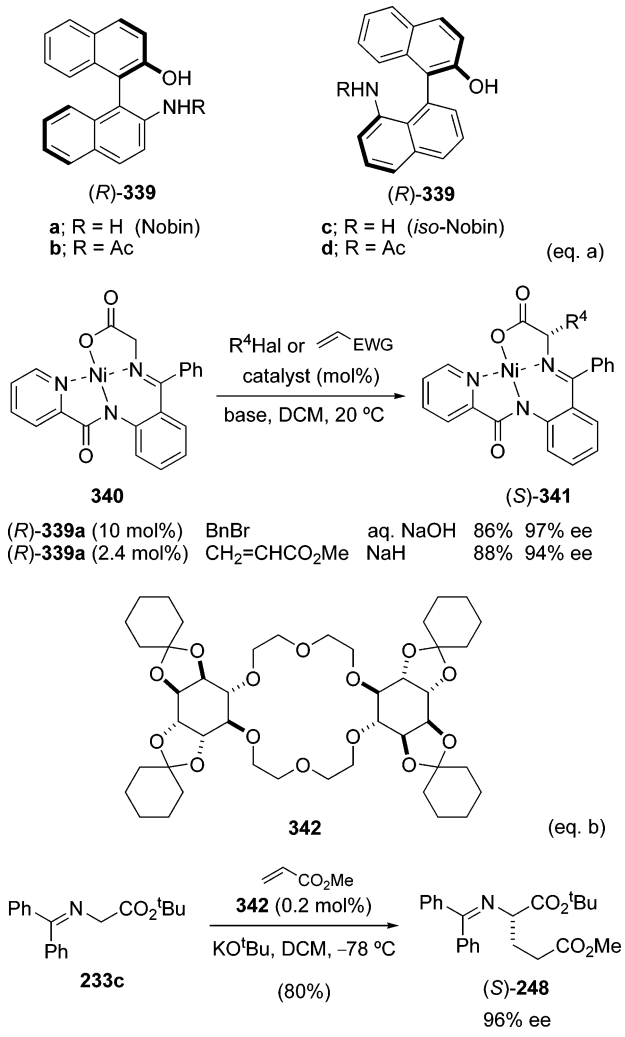
The asymmetric alkoxyallylation of azlactones using alkoxyallenes was a very interesting reaction catalyzed by a chiral palladium complex formed with the ligand (*S*,*S*)-**346**, widely used by Trost, furnishing excellent diastereo- and enantioselectivities. The final result of this transformation was an attack of the enolate at the more hindered allenic position and also represented a valuable alternative to the aldol-type processes (Scheme 50).[321] The pH of the reaction medium seems to be crucial and has to be carefully considered in each experiment because protonated palladium species must be generated for the formation of the allylic palladium complexes after the hydride transfer to the allene (Scheme 50).[321]

Activated enolates derived from 2-acetamido-1,3-dicarbonyl compounds **363** underwent efficient allylation reactions with (*R*)-Binap **87a** and (*R*)-**354** (*R*)-TMSBinap−palladium complexes (Scheme 51).[322,323] These compounds **364**, obtained with high ee (up to 93%), can be readily converted into various α-alkylated α-amino acid derivatives by employing several steps incorporating a very high functionality in the newly generated quaternary carbon atom.

The development of a new class of chiral P-chirogenic diaminophosphine oxides **355** (Figure 30) as ligand for many allylation process was used recently for imino esters and for 1,3-dicarbonyl compounds of the type **363**. In spite of working at room temperature, very large reaction periods were required for completion of the alkylation reaction of Schiff base **233c**.[324] The enantioselection (up to 84% ee) is sensibly lower than the enantioselectivity induced by (*R*)-Binap **87a** and its 4,4′-bisTMS-derivative (*R*)-**354**.

Stabilized enolates derived from compounds **365** and **366** and the nonstabilized zinc enolate **367** (Figure 31) were submitted to the palladium-catalyzed enantioselective allylation using different reaction conditions. With the starting material **365**, the allylation was carried out with (*R*)-Binap **87a**, affording the allylated product in moderate chemical yield (57%) and with a 46% ee.[325] Ferrocenylphosphines **356** and **357** (Figure 30) were evaluated in the palladium mediated asymmetric allylation reaction of α-nitropropanoates **366** under basic media, with ligand **357c** being the most efficient in this enantioselective reaction. For a better result (80% ee), this reaction needed sophisticated additives and bases, such as RbF and $RbClO_4$, and temperatures near −40 °C.[326] However, extraordinary diastereo- and enantioselections were registered in the reaction of Zn-enolate **367** in the presence of the ligand (*S*)-**358a**. In this example, the *anti*-**368** compound was obtained in 94% ee at room temperature and using a small amount of the π-allylpalladium complex

Scheme 44



chloride dimer (Scheme 52). The reverse steric course was achieved employing ligands **357**, obtaining 53% ee for the major isomer *syn*-**368**.[327]

Carroll rearrangement, a variant of ester Claisen rearrangement, is an efficient carbon−carbon bond forming reaction, which can be considered as an overall allylation reaction. This asymmetric transformation was achieved from α-acetamido-*β*-carboxylates **369** using a chiral palladium complex formed by the combination of $Pd_2(dba)_3CHCl_3$ and the ligand (*R*,*R*)-**349** (Figure 30). After carbon dioxide

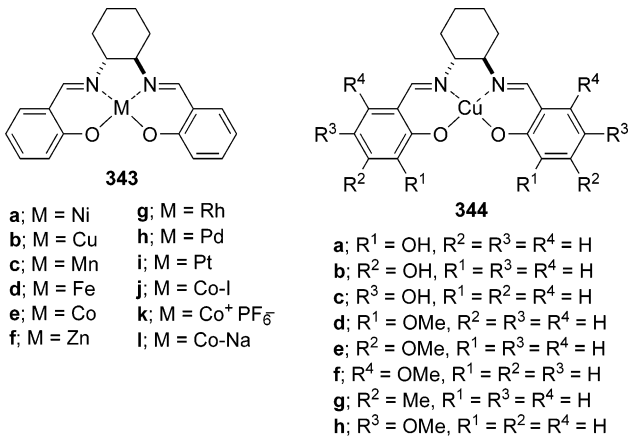
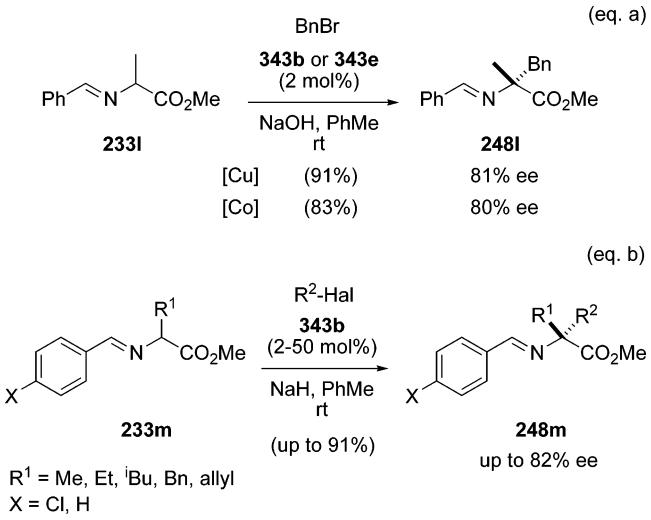


Figure 29. Chiral salen−metal complexes for the enantioselective alkylation of glycine or alanine derived enolates.

Scheme 45



liberation, an enolate is presumed to react onto the chiral *π*-allyl−palladium complex generated *in situ*. The final α-AA derivatives **370** were obtained in good to moderate yields and good enantioselectivities (up to 90% ee) under very mild reaction conditions (Scheme 53).[328]

Another chiral metal-catalyzed addition reaction of glycine derivatives deals with isocyanoacetates or isocyanoacetamides.[3x] The direct attack of isocyanoacetates **371a** onto various aldehydes is often mediated by a cationic Au(I) complex. This reaction was first reported by Hayashi's group, and in fact, it is considered as the first catalytic enantioselective aldol-type reaction[329] (Scheme 54). The 1,3-prototropic shift would give an enolate intermediate able to trigger the aldol-cyclization sequence. The most suitable ligands for this transformation were chiral ferrocenes **372b** and **372c**. The final hydrolysis of the *trans*-oxazolines **373** afforded *threo*-*N*-formyl-*β*-hydroxy-α-amino acid esters **374**. Originally, the main inconvenience of this methodology was the formation of the 4-epimer to give *cis*-oxazolidine **373**, which has been isolated in very low optical purity. However, this difficulty was overcome using determined fluorinated benzaldehydes; for example, 2,3,5,6-tetrafluorobenzaldehyde furnished compound *trans*-**373** (R = 2,3,5,6-F_4C_6H-) as the major diastereoisomer in 93% yield and 90% ee.[330] In this work, it was deduced that the enantiodiscrimination was powerfully controlled by the number of fluorine atoms bonded to the arene of the employed fluorobenzaldehyde. This elegant methodology, using chiral complexes (*R*,1′*S*)-**372b** and (*S*,1′*R*)-**372c**, was exploited in the synthesis of the enantiomerically enriched (−)-*β*-hydroxylisine **375**[331] and for the elaboration of the heterocycle **376**, a chiral intermediate used in the synthesis of (−)-α-kainic acid,[332] respectively.

N-Sulfonyl imines, derived from aromatic aldehydes, underwent the addition reaction of ethyl isocyanoacetate **371b** catalyzed by chiral complex (*S*,1′*R*)-**372b**. Here, a reversal diastereoselection was detected with respect to the analogous aldol reaction. The *cis*-**377** was generated as the major isomer in high yields and with both good de and ee (Scheme 55). As an application of this Mannich-type reaction, α,*β*-diamino esters **378** were isolated after hydrolysis in very good yields. Surprisingly, the methyl isocyanoacetate **371a** gave a poor ee of the corresponding *cis*- and *trans*-**377** heterocycles.[333]

α-Isocyanoacetamide **379** was allowed to react with fluorinated aldehydes, such as was described previously for

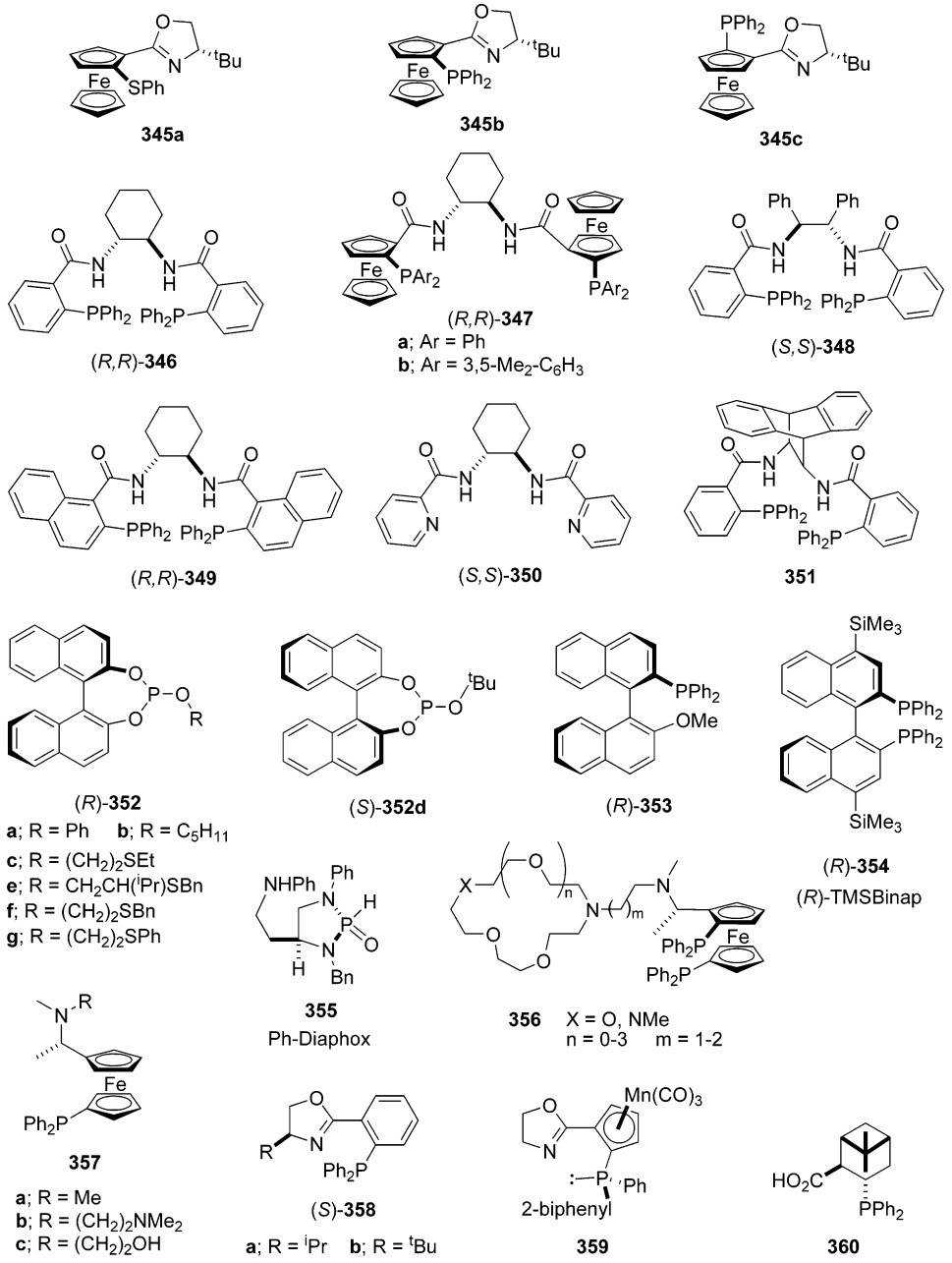
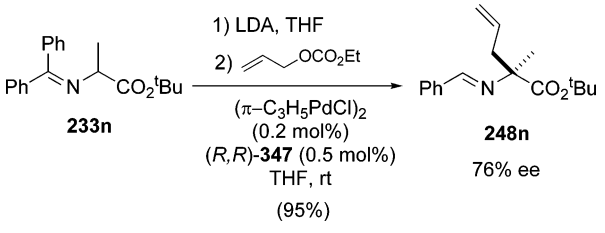


Figure 30. Chiral ligands or organocatalysts **345**−**360** employed in the palladium-catalyzed enantioselective allylation of enolates of glycine and its derivatives.

Scheme 46

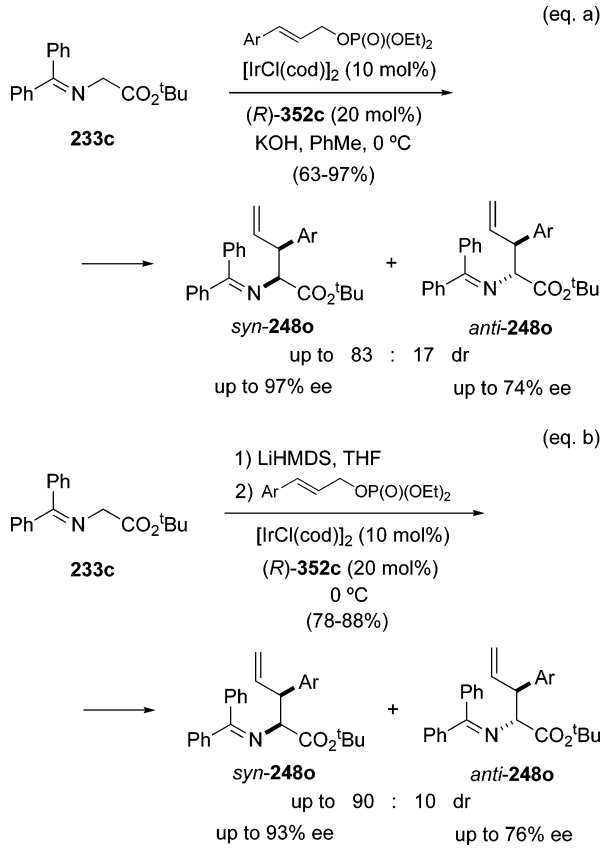


methyl isocyanoacetate **371a**.[330b,334] This reaction provided the preferential formation with high ee's of *trans*-oxazolines **380** regardless of the fluoro-substituted benzaldehyde used. Serine derivatives **381** were also isolated in very high ee from the corresponding product *trans*-**380** after hydrolysis employing 6 N HCl (Scheme 56).

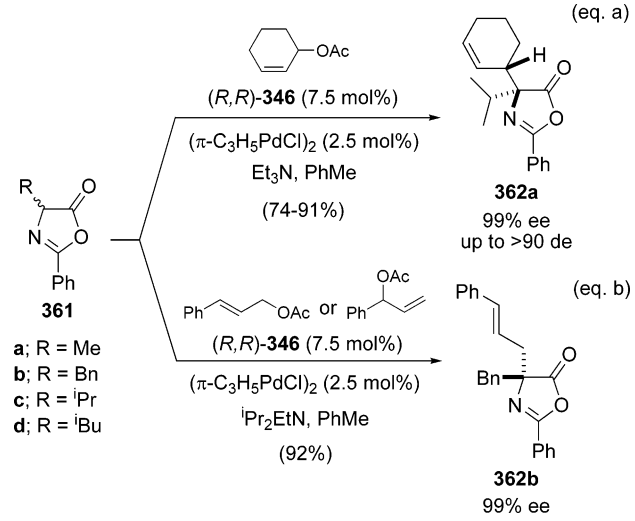
A very frequent practice in chemistry is the evaluation of the catalytic activity of the newly synthesized pincer-type Pt, Pd, or Rh complexes in the asymmetric aldol reaction between α-isocyanoacetate **371a** and aldehydes (see the reaction of Scheme 54).[335−344] All of the chiral complexes depicted in Figure 32 were introduced in the reaction mixture in rather small amounts (1−1.5 mol %), obtaining very different results of the major product *trans*-**373**. Despite the high *trans*-selectivity, the enantioselectivity was rather low or moderate, with the most interesting results being achieved with Pt complexes **382**[335] and **390**.[343] The Rh complexes **391** were employed in stoichiometric amounts in the same aldol reaction, giving, after treatment with Ag(I) salts, the corresponding *trans*-oxazolines **373** as major products, but the substoichiometric catalytic version has not been reported yet.[344]

To the best of our knowledge, there is only one example reported in the literature dealing with the enantioselective aldol reaction involving an isothiocyanoacetate derivative. This compound **392** was used in the direct catalytic enan-

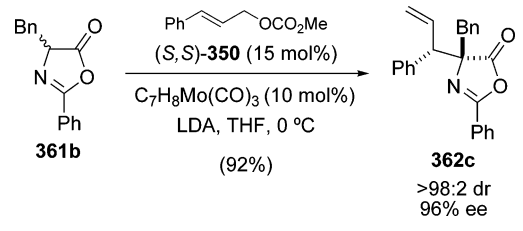
Scheme 47



Scheme 48

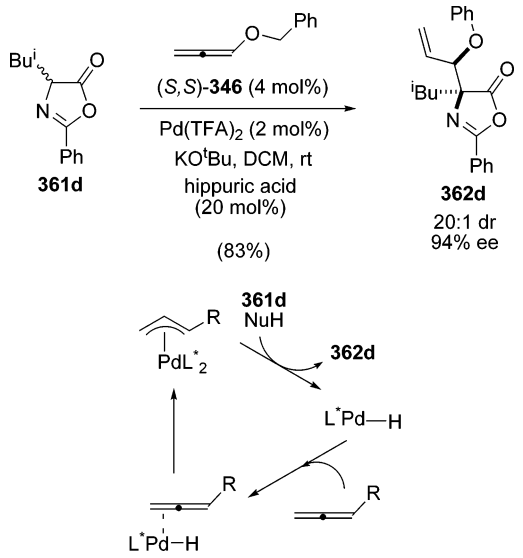


Scheme 49

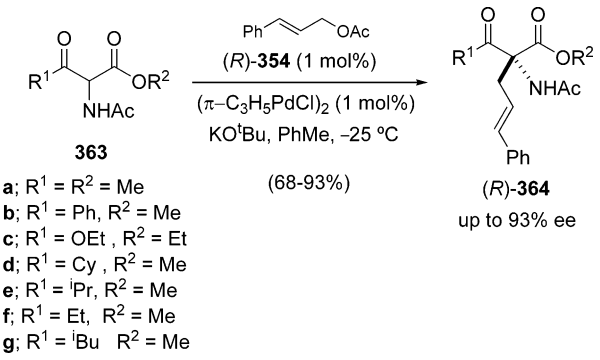


tioselective synthesis of protected aryl β-hydroxy-α-amino acid surrogates **393**. PyBox **176** or Box **181** ligands (see Figure 20) were evaluated in the aldol reaction mediated by magnesium perchlorate at −78 °C. The best enantioselection observed for products **393** was achieved by using 10 mol %

Scheme 50



Scheme 51



of the $Mg(ClO_4)_2$−(*R*,*R*)-**176c** complex (Scheme 57). The oxazolidinone residue was finally removed from the structure by $Mg(OEt)_2$, generated from anhydrous ethanol and methylmagnesium bromide, but any further transformation was reported in order to achieve the corresponding serine analogues.[34553]

4.1.3. Catalyzed Additions of 5-Methoxyoxazoles

The addition reactions of the corresponding enolates generated from 5-methoxyoxazoles **394** onto aldehydes, also called the Suga−Ibata reaction,[346] are a very interesting straightforward synthesis of 2-oxazoline-4-carboxylates. This overall transformation can be considered as a formal [3+2] cycloaddition reaction of the oxazole ring and the aromatic aldehyde, where the resulting alkoxyde intermediate **I** originates from the definitive ring closing−ring opening sequence (Scheme 58).

The first catalytic enantioselective Suga−Ibata reaction was reported in 1998[347] using a chiral Binol−AlMe complex

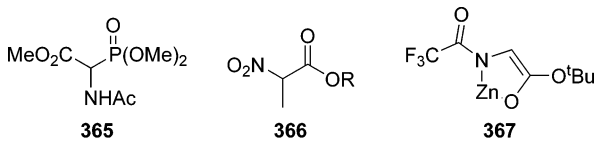
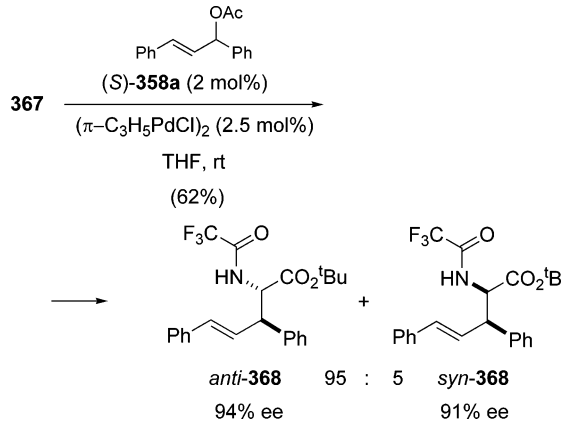
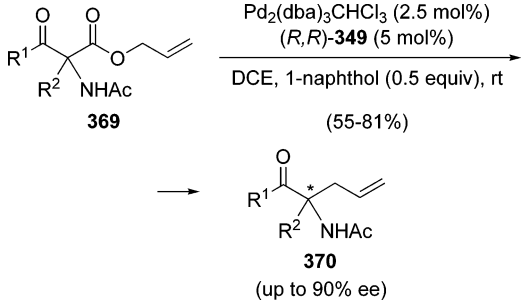


Figure 31. Other substrates used as nucleophiles in the palladium catalyzed enantioselective allylation reactions.

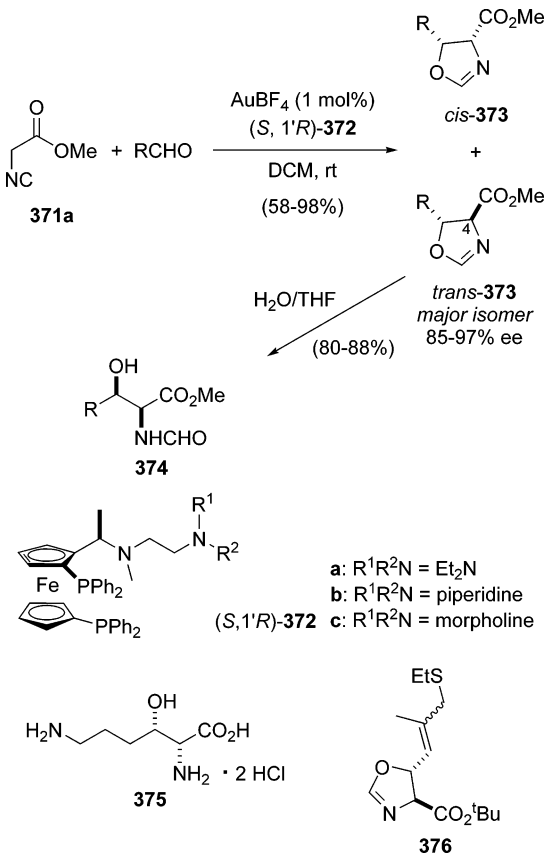
Scheme 52



Scheme 53

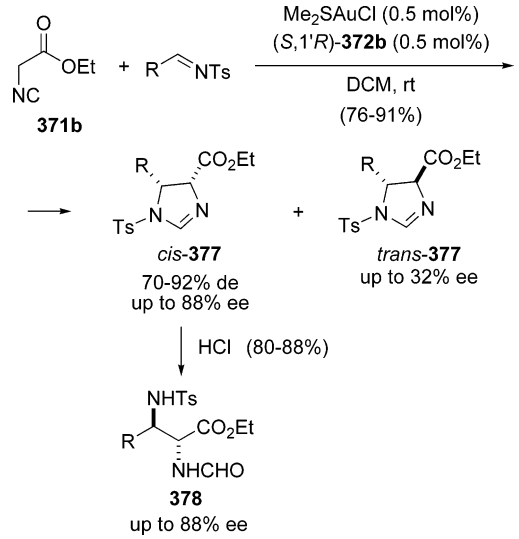


Scheme 54

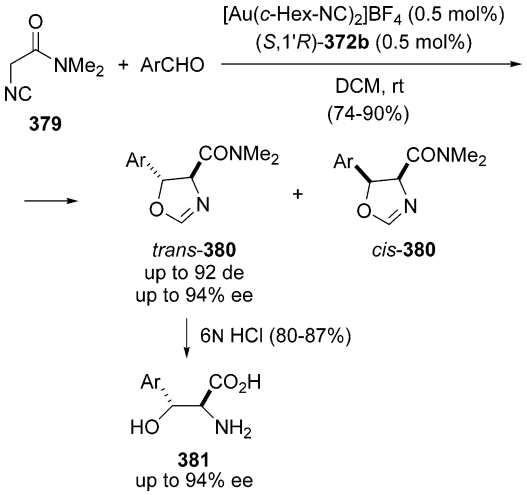


395 (30 mol %). The *cis*-oxazoline **396** was always the major product obtained, and in many instances, the *trans*-**396** heterocycle was not detected in the crude reaction mixture. This *cis*-selectivity can be originated by initial π-stacking interactions favoring minimal repulsions between substituents.[347b] The *threo*-β-phenylserine **397** was prepared and isolated as a free α-amino acid for demonstrating the application of the method to the synthesis of the mentioned natural products and also for determining the absolute configuration of the two stereogenic centers generated during the process.[347b] The chiral complex **395** gave the best enantioselections and *cis*/*trans* ratios of compounds **396** in spite of several 3,3′- or 6,6′-disubstituted chiral Binol−Al complexes being essayed.[347b]

Scheme 55



Scheme 56



Chiral salen−aluminum complexes **398c** and chiral **181a**−Cu(II) complexes also gave high *cis*-diastereoselectivities and very good enantioselections by reaction with aromatic aldehydes (Scheme 59, eq a) and with ethyl glyoxylate (Scheme 59, eq b), respectively. In eq a of Scheme 59, the *cis*-oxazoline **396** was epimerized to the corresponding *trans*-**396** oxazoline employing a substoichiometric amount of DBU in very high yield and very good diastereoselectivity (90% de).[348]

In these reactions, the nature of the catalytic complex has a high relevance. When the catalysts were $SnCl_4$, $TiCl_4$, or $AlCl_2Me$, the *trans*-3-oxazoline was the dominant product. However, when bulkier catalysts such as Binol−AlMe or salen−aluminum complexes were used, the final major product was the *cis*-oxazoline. PM3,[348] B3LYP/6-31G*,[349] and DFT at B3LYP/6-31G*[350] calculations have been used

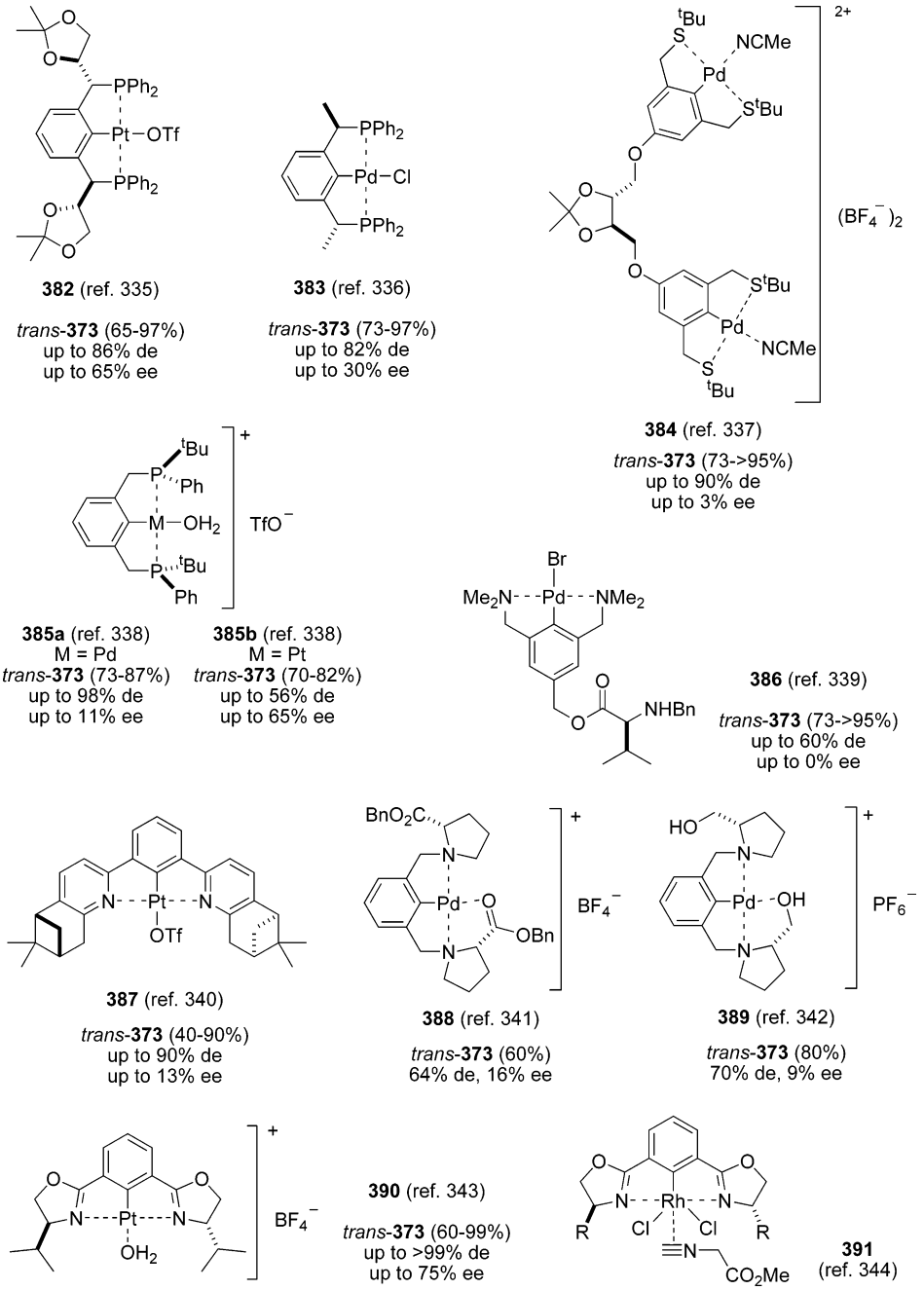
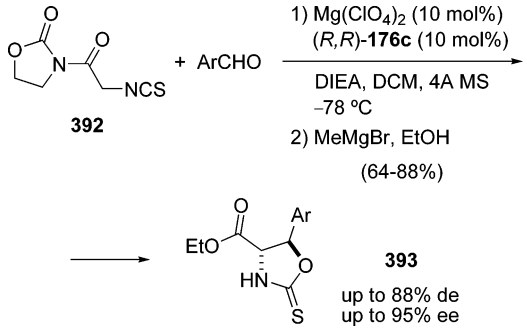


Figure 32. Pincer-type complexes tested in the asymmetric aldol reaction with α-isocyanoacetate **371a**.

Scheme 57



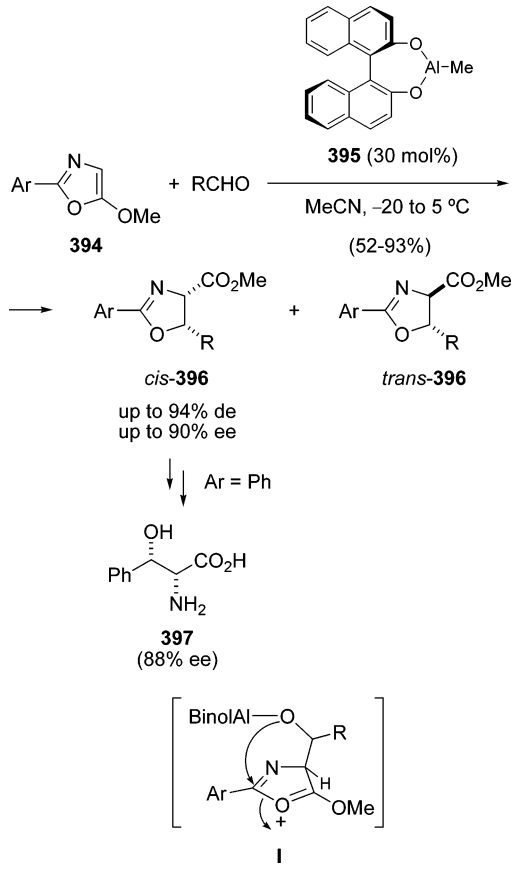
to study the mechanism and the regio- and the stereochemistry of these Lewis acid-catalyzed reactions. Probably, the process occurred via a stepwise sequence, starting from the nucleophilic addition (aldol reaction) as shown in structure **I** of Scheme 58. This step is followed either by a concerted ring-opening−ring-closing step or by ring-opening and ring-closing steps. In addition, electronic effects between heteroatoms can direct the *cis*- or *trans*-diastereoselectivity, which is also dependent on the solvent, substituents, and catalyst employed.

4.1.4. Rearrangements of O-Acylated Azlactones

The rearrangement of *O*-acylated azlactones **400** (also called Steglich−Höfle rearrangement) is promoted by *N*,*N*-dimethylaminopyridine (DMAP) and 4-(pyrrolidino)pyridines (PPY), furnishing a new carbon−carbon bond and a new quaternary stereocenter.[351a] The resulting azlactones **401** possessed a very crowded functionalization at the quaternary carbon atom and constituted very interesting precursors of α-alkylated α-aminomalonic acid.

The first enantioselective construction of this quaternary stereocenter was published by Fu's group, designing a new

Scheme 58

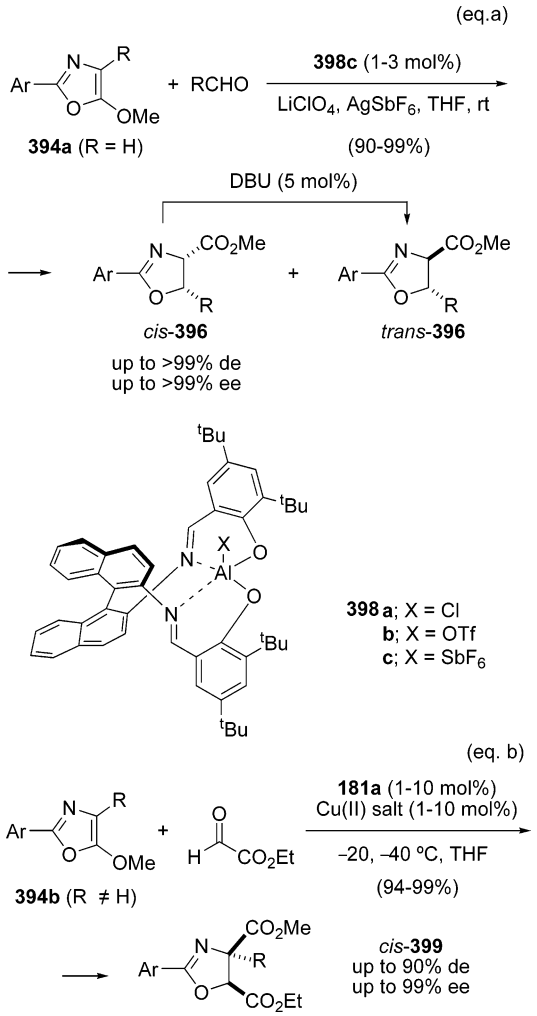


family of planar quiral derivatives of DMAP, **402** and **403** (PPY*).[351b] Both types of catalysts were tested in the rearrangement of azlactones **400** at 0 °C (Scheme 60, eq a), unveiling that benzyl carbonates **400** (R = Bn) were the more appropriate substrates for this enantiodiscrimination promoted by organocatalyst **403**. This transformation allowed the presence of a wide range of substituents R^2, obtaining products **401** in very high both chemical yields and ee's (Scheme 60, eq b).

Preliminary studies indicated that the rate of the rearrangement is zero-order in substrate and independent of the concentration. This observation was consistent with the pathway shown in Scheme 61, wherein the resting state of the system is the ion pair. Products **403** are configurationally stable under the reaction conditions, which provided evidence that step B of Scheme 61 is irreversible.[351,352]

Chiral organocatalysts **404**−**407** (Figure 33) were also tested as activating agents of the rearrangement of azlactones **400**. Chiral DMAP derivative **404**, in general, provided slightly higher ee (up to 95%) than the chiral phosphine **405** (up to 92% ee), although the chemical yields were identical.[353,354] When ferrocenyl ligand **406** was allowed to catalyze the asymmetric reaction described in Scheme 60, a very low enantioselection was obtained (up to 25% ee) in good yields (up to 69%).[355] The nonracemic ferrocene **406** was also essayed in the dynamic kinetic resolution of azlactones (via enantioselective protonation), giving rise to very disappointing results (up to 42% ee, see section 2.4). On the other hand, cobalt metallocene **407** induced moderate enantiodiscrimination in this model reaction (up to 76% ee) when toluene was used as solvent at 0 °C, and any improvement of the ee was observed when decreasing the temperature to −20 °C.[356]

Scheme 59

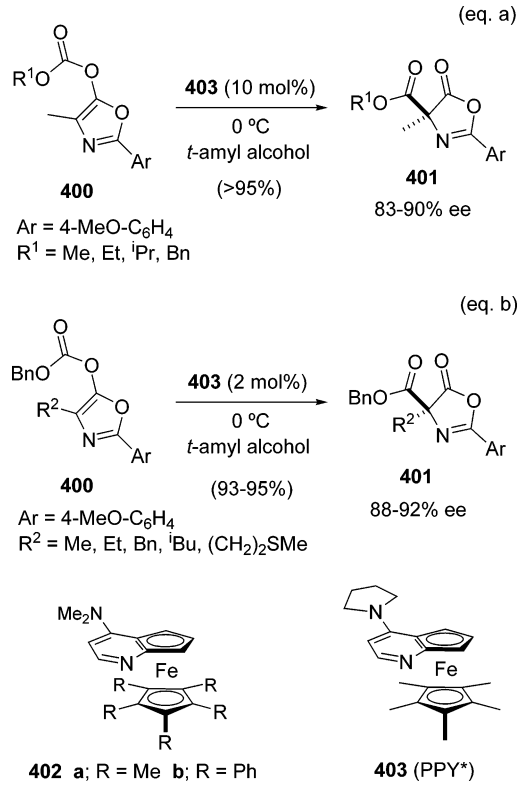


From all of the examples described in this section, no hydrolysis to final α-AAs was carried out. However, the synthesis of lactones and lactams by functional group transformations at the α-side chain and at the carbonyl group has been described.[354] Catalysts **403**, **404**, and **405** were the most efficient organocatalysts for the synthesis of azlactones **401** using very low catalyst loadings (1−2 mol %).[351−356]

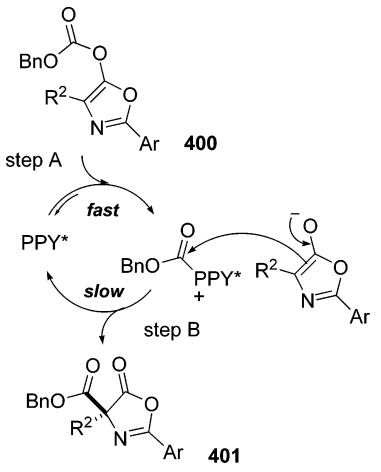
4.2. Nucleophilic Alkylations of α-Imino Esters

The α-imino esters are very important precursors of α-AAs, as was discussed in the hydrogenation reaction used for introducing enantioselectively the α-hydrogen atom (section 2.2). In this part, these α-imino esters, acting as very versatile electrophiles, are incorporated in catalytic asymmetric reactions, providing a vast array of α-AA derivatives according to the general addition reaction depicted in the Scheme 1 (eq j). Due to the low reactivity of the imines (in comparison with the more reactive carbonyl group), their electrophilicity is usually enhanced by the presence of an activating agent of the nitrogen atom (typically a Lewis acid). The general eq j of Scheme 1 can be unfolded according to the synthesis of α-AA derivatives into Scheme 62. Chiral organocatalysts and chiral metal complexes are currently involved in the enantioselective addition reactions shown in Scheme 62, and a large amount of processes dealing with these types of asymmetric transformations are know.[160,357] For example, the simple allylation reaction with allyltin

Scheme 60



Scheme 61



reagents and allylsilanes was catalyzed by chiral copper or zinc complexes and by chiral organocatalysts such as sulfoxides and bisphosphine oxides (Scheme 62, eq a). Ene reactions using chiral copper catalysts (Scheme 62, eq b) were also studied, obtaining equivalent products to those described in eq a, so in both cases allylic α-AAs can be generated. The enantioselective arylations were developed under different reaction conditions, with the copper-catalyzed enantioselective arylation from arenes being the most employed sequence to afford arylglycines (Scheme 62, eq c). Mannich-type reactions are also very interesting transformations because they provide direct precursors of AAs and can be performed with similar efficiency by chiral organocatalysts or chiral organometallic complexes (Scheme 62, eq d).

This general overview has been continuously developed, and during the past few years, new chiral entities were able to construct new carbon−carbon bonds, mainly through

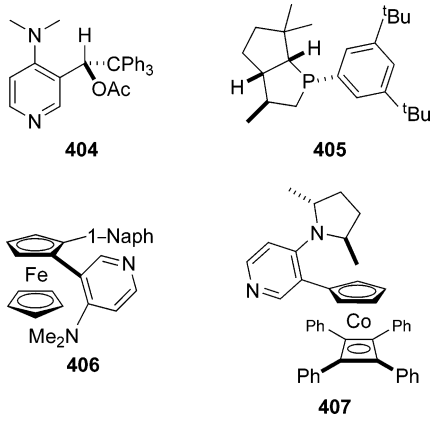


Figure 33. Ligands **404**−**407** employed in the enantioselective rearrangement of *O*-acylated azlactones.

Mannich-type and aza-Henry reactions, thus obtaining valuable poly functionalized α-AAs and other chiral building blocks.[160] Since the preceding review covering the comprehensive reactivity of α-imino esters,[160] Mannich-type reactions (Scheme 62, eq d) have been extensively studied rather than other enantioselective reactions due to the functional diversity of the achieved products and the mild reaction conditions required. Next, we will distinguish the reaction performed with metal complexes and the analogous reaction performed in the presence of organocatalysts as follows.

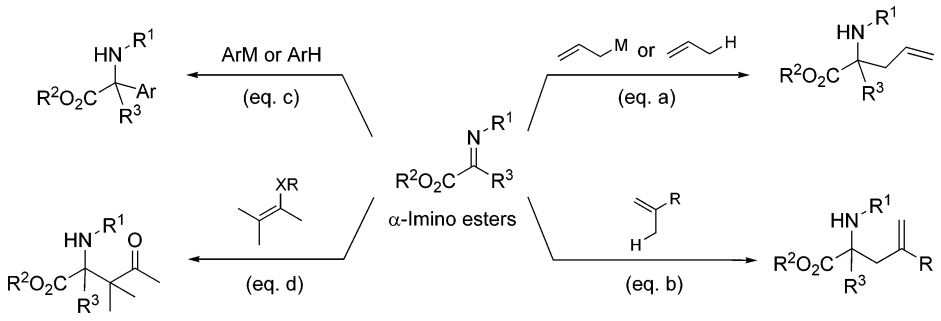
4.2.1. Allylations

Allylic amino acid derivatives can be obtained by reaction of α-imino esters with allylsilanes or stannanes. The allylation of glyoxylic *N*-tosylimines was independently reported by Lectka's[358] and Jørgensen's[359] groups working with similar (R_a)-*p*-Tol-Binap **144**−[Cu] complexes (Figure 17). Allylsilanes **409** were successfully utilized as allylating agents in the presence of a catalyst formed by copper(I) perchlorate at −78 °C and the chiral phosphine in DCM. The resulting products **410** were obtained in very high yields and with important enantioselections (up to 93% ee) and good diastereoselectivity (up to 20:1, *anti*/*syn* ratio) (Scheme 63, eq a).[358] However, allylstannanes **411** proved to be better allylating reagents than the allylsilanes in the presence of $CuPF_6$ instead and the same phosphine in toluene at −78 °C. In this reaction, the *syn*-diastereoisomers were isolated as major compounds in very high enantioselections (up to 89% ee) (Scheme 63, eq b), unlike the previous reaction performed in DCM.[359] Allylsilanes did not afford as good results as the reported ones in eq a, indicating the crucial effect of some parameters such as copper(I) salts and solvents in this particular transformation.

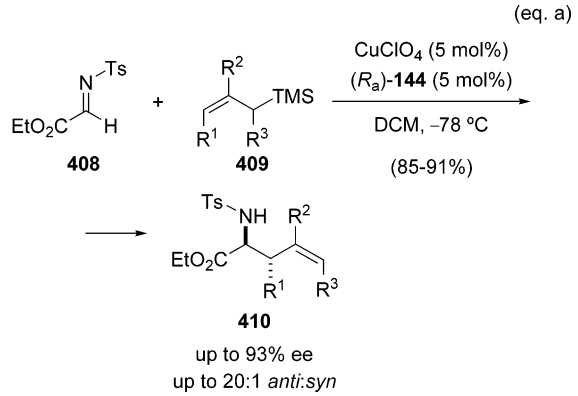
The first example of the catalytic asymmetric allylation of glyoxylic hydrazones was achieved using 4-methoxybenzoylhydrazone **412**. The reaction took place in aqueous media using a catalytic amount of ZnF_2 (20 mol %) and a chiral amine **414** (Ar = 2-MeO-C_6H_4, 10 mol %) as ligand (Scheme 64). The allyltrimethoxysilane **413** was employed in this enantioselective transformation (up to 85% ee), where the fluoride anion is presumed to be necessary in order to furnish a very good chemical yield of products **415**, by increasing the nucleophilicity of the allylic system.[360] Adducts **415** were obtained in up to 85% ee, although they have not been further transformed into the corresponding amino esters.

The first example of an organocatalytic stereospecific and enantioselective allylation of hydrazones **416** was published

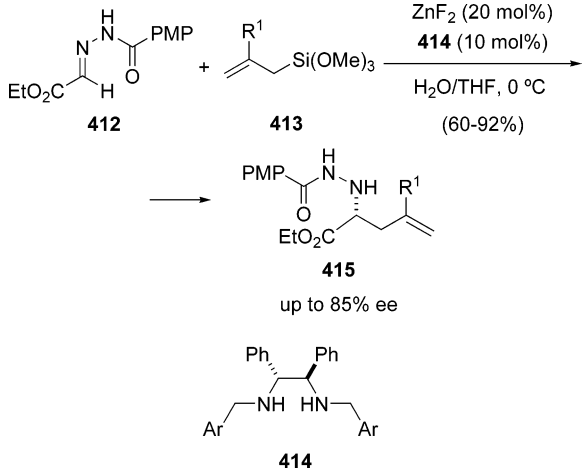
Scheme 62



Scheme 63

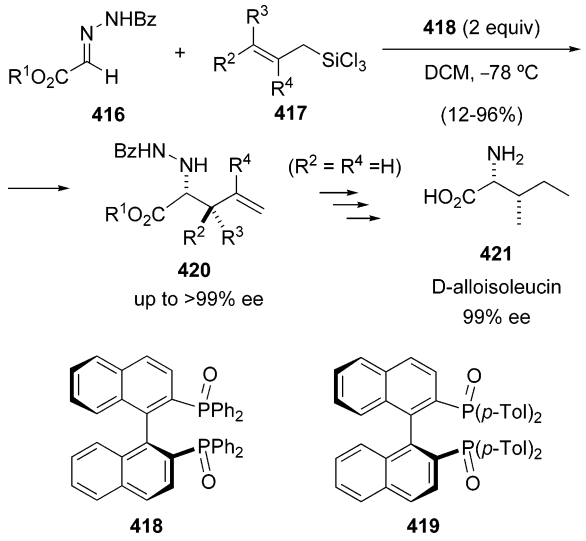


Scheme 64

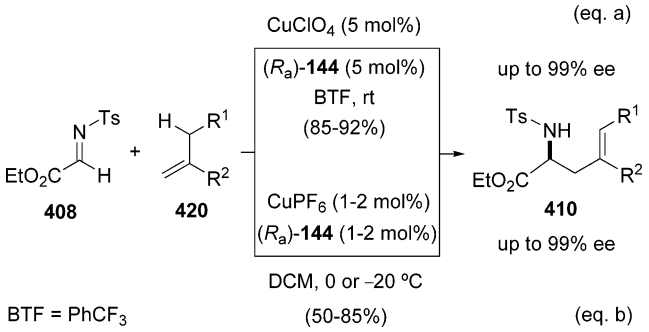


by Kobayashi's group. Both organocatalytic bisphosphine oxides **418** and **419**, introduced in excess (2 equiv) with respect to the α-imino ester **416**, gave identical enantioselection of the allylation reaction carried out with allyltrichlorosilanes **417**. The resulting ee of the product **420** was very high (up to >99% ee), and excellent *syn*/*anti* diastereoselection was obtained depending on the substituents of the allyl system (Scheme 65).[361] This reaction was successfully applied to the enantioselective synthesis of D-alloisoleucine **421**, an uncommon α-AA identified as part of biologically important peptides.[361]

Scheme 65



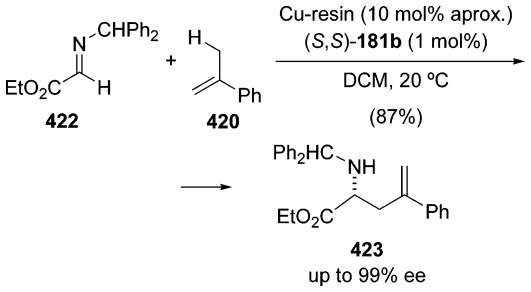
Scheme 66



4.2.2. Ene Reactions

Another type of alkenylations underwent by the α-imino esters, different from the allylation reactions described before, are the ene reactions (Scheme 62, eq b). As well as occurred in allylations, Lectka's[358b,362] and Jørgensen's[363] groups developed simultaneously the ene reaction of *N*-tosylimine **408** using the same chiral copper catalysts described in Scheme 63. The different reaction conditions shown in Scheme 66 provided very close results in terms of chemical yields (50−92%) and enantioselections (up to 99% ee in both

Scheme 67



cases). In the reaction involving Cu(I) perchlorate, compounds **410** were obtained in the presence of a nonfrequently used solvent such as trifluoromethylbenzene (BTF), able to dissolve the (R_a)-*p*-Tol-Binap **144**−$CuClO_4$ complex, allowing the reaction to proceed at room temperature (Scheme 66, eq a).[358b,362] By contrast, a more conventional solvent such as DCM, using lower temperatures (−20 or 0 °C), was preferred for the ene reaction between **408** and **420**, employing $CuPF_4$ as copper salt and (R_a)-*p*-Tol-Binap **144** as chiral ligand (Scheme 66, eq b).[363]

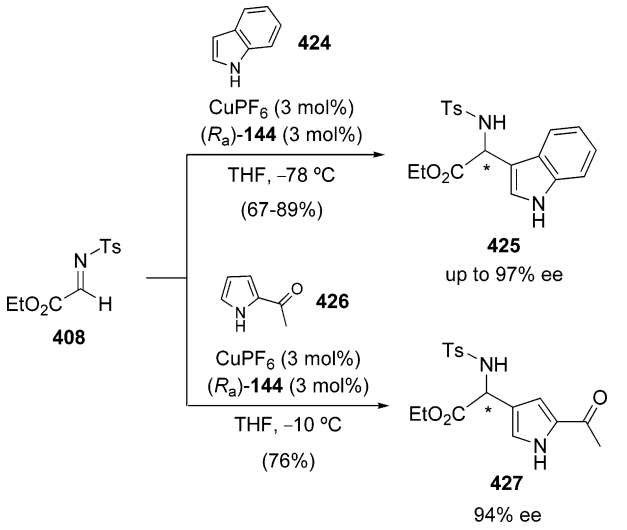
The complex formed by the mixture of an immobilized Cu-exchanged zeolite and the bisoxazoline ligand (*S*,*S*)-**181b** (Figure 20) was successfully implemented in the reaction of *N*-benzhydryl α-imino ester **422** with α-methylstyrene **420** (R^1 = H, R^2 = Ph). Product **423** was isolated in good chemical yield (87%) and high enantioselectivity (90% ee) after 20 h of stirring at room temperature (Scheme 67).[364]

4.2.3. Arylations

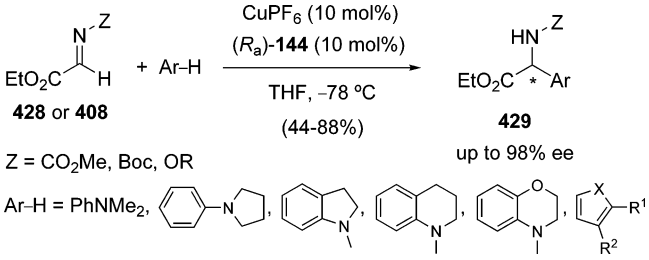
The enantioselective aryl-transfer reactions to imines, *via* an appropriate aryl−metal intermediate or by a direct asymmetric addition of electron-rich aromatic or heteroaromatic compounds (aza-Friedel−Crafts reaction) (Scheme 62, eq c), offer straightforward approaches to biologically active arylglycine derivatives. For example, the optically active α-aryl or α-hetroaryl α-AAs, which have been relatively complicated to synthesize, can be generated in high ee through this valuable strategy. Despite their potential, a relatively limited number of reports on asymmetric aryl transfer reactions to α-imino esters have been presented.[160] The first report of an enantioselective aza-Friedel−Crafts reaction of imines was reported by Johannsen's group.[365] The complex formed by (R_a)-*p*-Tol-Binap **144** (Figure 17) and $CuPF_6$ catalyzed the enantioselective addition of electron-rich aromatic compounds such as indoles **424** and 2-acetylpyrrole **426** onto *N*-tosylimino esters **408**. The chemical yields of compounds **425** and **427** are good, and the enantiomeric excesses are excellent in both examples (Scheme 68).[365] The pyrrole derivative **426** reacted at higher temperatures than the indoles **424** did.

Jørgensen's group also reported the use of the already mentioned (R_a)-*p*-Tol-Binap (**144**)−$CuPF_6$ complex in the enantioselective Friedel−Crafts reaction of several glyoxylic imines **428** with electron-rich aromatic compounds.[366,367] In general, the reaction occurred in high yields (68−91%) and with high enantioselections (up to 98% ee) except in the case of *N*-Boc protected substrate, where, albeit in high yield, only moderate enantioselectivity (64% ee) was achieved. The absolute configuration of the products **429** was dependent on the nature of the *N*-protecting group; thus, *N*-ethoxy, *N*-methoxy, and *N*-Cbz protected imines gave the (*R*)-enantiomers, whereas the more sterically hindered *N*-Boc and

Scheme 68



Scheme 69



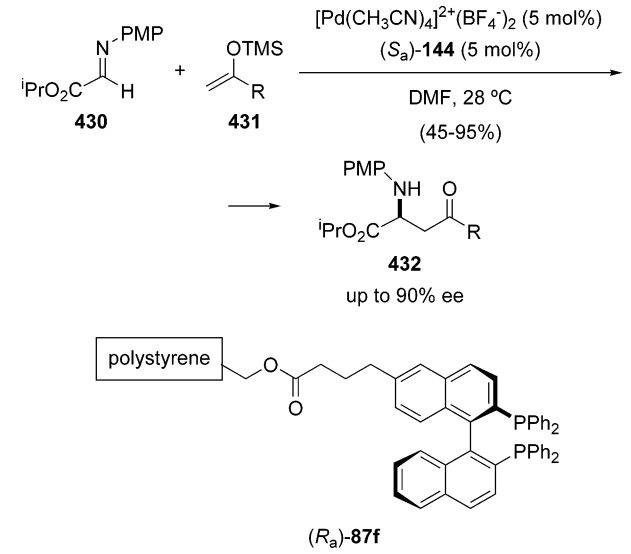
N-tosyl protected substrates **428** provided products with (*S*)-configuration (Scheme 69). The presumed mechanism involved the attack of the arene onto the activated pair formed by the Lewis acid and the imine, taking the place of the carbon−carbon bond forming sequence followed by the final rearomatization.

4.2.4. Mannich-Type Reactions

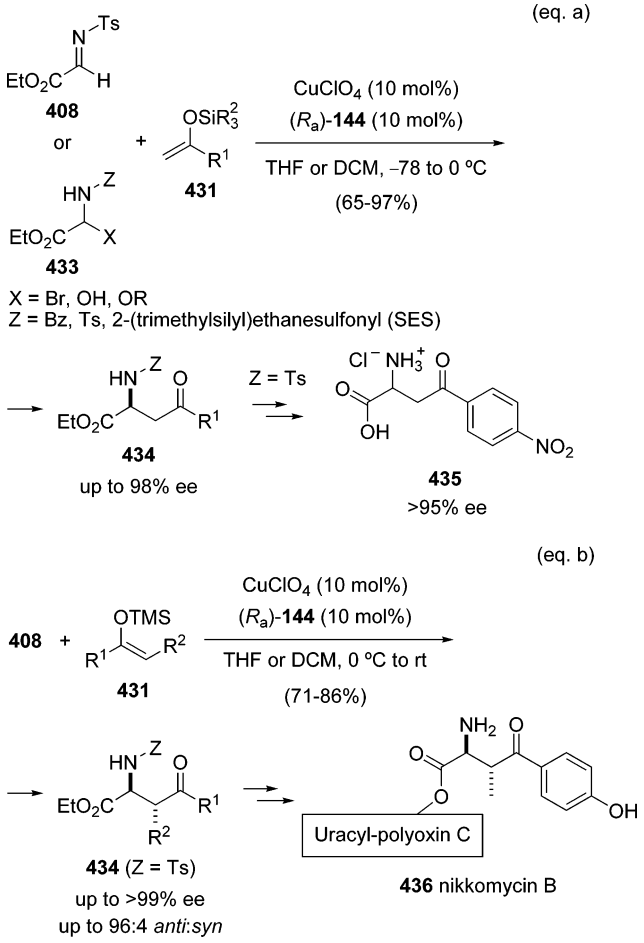
In this section we will consider the Mannich-type reactions performed with chiral metal complexes and with chiral organocatalysts. Although the Mannich reaction between imines and silyl enol ethers has been known as a powerful method for carbon−carbon bond formation for a long time, only recently have the metal complex-catalyzed enantioselective reactions been developed. Sodeoka's group described in 1998 the reaction of the glycoxylic imine **430** and trimethylsilyl enol ethers **431** catalyzed by the binuclear (S_a)-Binap **87a**−Pd(II) (Figure 13) or (S_a)-*p*-Tol-Binap **144**−Pd(II) complexes. The best results of compounds **432** (up to 90% ee) were achieved using ligand (S_a)-*p*-Tol-Binap **144** in DMF at 20 °C and in the presence of small amounts of base in order to scavenge the *in situ* formed HBF_4 (Scheme 70).[368,369] Based on evidence from ^{1}H NMR and ESI-MS analysis, a *O*-bound palladium enolate can be considered as the species able to enantiodiscriminate both faces of the α-imino ester.[369] The polymer supported version of this catalyst was also designed from a polystyrene-linked Binap **87f**. When the (R_a)-**87f**−Pd(II) complex was tested in the analogous Mannich-type reaction between **430** and **431**, it was found to give somewhat lower enantioselectivity in compound (*S*)-**432** (up to 76% ee).[370]

At about the same time, Lectka's group developed a similar Mannich reaction between trimethylsilyl enol ethers, derived from aryl methyl ketones, and *N*-tosylimines **408**.[371]

Scheme 70

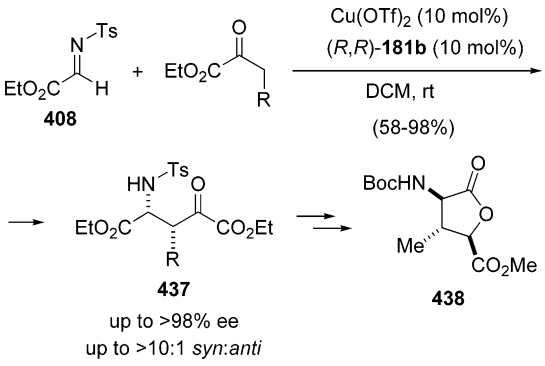


Scheme 71



A number of Binap−metal complexes such as Ag, Pd, Cu, and Ni were tested, with the (R_a)-Tol-Binap **144**−$CuClO_4$ complex being the more appropriate catalytic system. In this way, γ-oxo α-AA derivatives **434** were obtained in good yields and with excellent enantioselection (up to 98% ee) when the reaction was carried out in THF or DCM from −78 to 0 °C (Scheme 71, eq a).[358b,371] Interestingly, regardless of the geometry of the silyl enol ethers **431**, *anti*-products **434** were always obtained in good diastereoselectivities (up to 96:4 *anti*/*syn* dr) and enantioselectivities (up to >99% ee) under the analogous reaction conditions described before for eq a (Scheme 71, eq b).[358b,372] In these reactions, the copper enolate intermediate could not be detected by ^1H NMR spectroscopy; therefore, the catalyst was believed to act as a chiral Lewis acid coordinating and activating the imine **408**, such as demonstrated in the IR spectroscopy experiments.[372] The compound **434** (R^1 = 4-HO-C_6H_4) was considered as a potential precursor of the non-natural segment of the antibiotic nikkomycin B **436**. Alternatively, aminal derivatives **433** have been employed for the *in situ* generation of the corresponding *N*-protected α-amino esters by intermediacy of the copper catalyst. The catalyst served a dual role, namely to dissociate X^- and, subsequently, to activate the newly generated imino ester. Compounds **433** were obtained with exactly the same yields and enantiomeric excesses as those observed in the reaction using directly the α-imino ester **408**.[373] Starting from the three *N*-protected systems **433** (*Z* = Bz, Ts, and SES), L-3-nitrobenzoylalanine **435** was prepared as a pure enantiomer, evaluating the different deprotection conditions required for each electron-withdrawing group (Scheme 71, eq a). This molecule **435** is currently one of the best inhibitors of kynurenine-3-hydroxylase and kynurenunase.[358b]

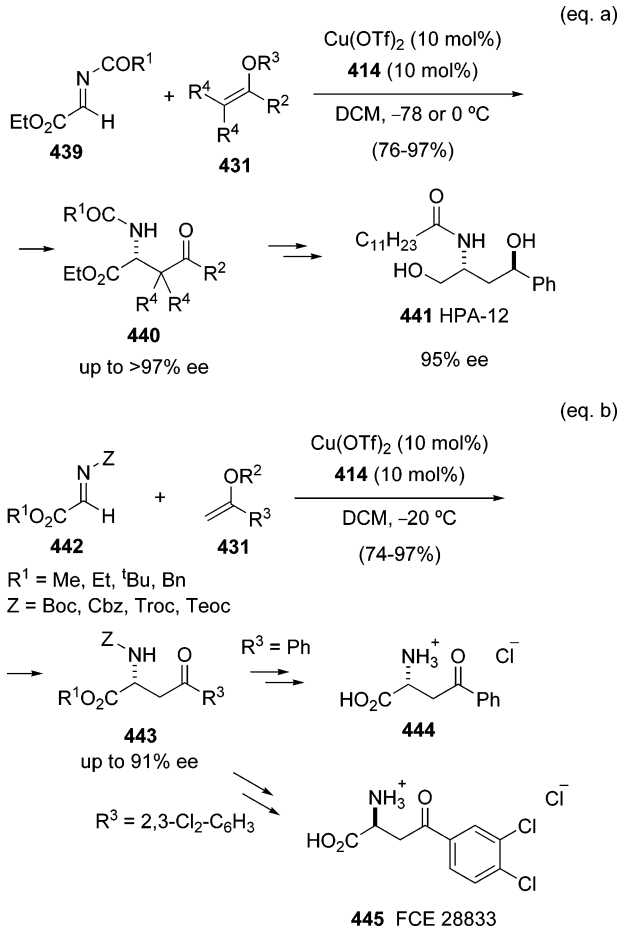
Scheme 72



A highly enantioselective Mannich-type reaction of α-keto-esters and α-imino ester **408** was performed at room temperature in the presence of the chiral copper complex generated from (*R*,*R*)-Ph-Box **181b** (Figure 20) and $Cu(OTf)_2$. The excellent enantioselection (up to >98% ee) and the very high *syn*-diastereoselectivity obtained for compounds **437** is described in Scheme 72.[374] These 4-oxoglutamic acid ester derivatives **437** were converted into highly functionalized, optically active α-amino-γ-lactones **438** after a three-step sequence. Again, the chiral copper complex acts as catalyst in the formation of the enol and coordinates the imine by two positions, with the reaction taking place in the inner sphere of the metal center.[374]

N-Acylimino esters **439** reacted with silyl enol ethers **431** to afford the corresponding Mannich-type adducts **440** in high yields and with high enantioselectivities (up to 97% ee). A wide variety of silyl enol ethers derived from lactones, as well as esters and thioesters, reacted smoothly at −78 °C for *N*-benzoyl imines or at 0 °C for *N*-acetyl- or *N*-alkylcarbonyl imines. The selected copper complex was obtained by mixing $Cu(OTf)_2$ and chiral ligand **414** (Ar = 1-naphthyl) (Scheme 73, eq a).[375,376] Apart from silyl enol ethers **431** (R^3 = TMS), alkyl vinyl ethers **431** (R^3 = Me) were also tested, giving very good results of both yields and ee's of products **440**. In these works, chiral aminodiol HPA-12 **441**, a new inhibitor of ceramide trafficking from the endoplastic reticulum to the site of sphingomyerin synthesis,

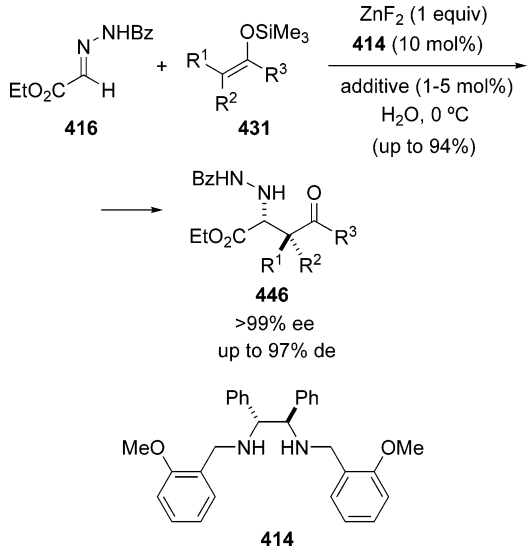
Scheme 73



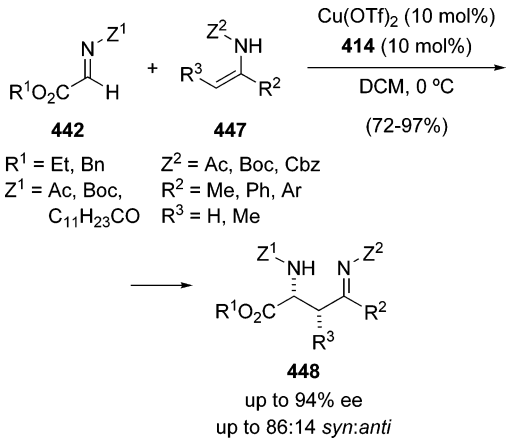
has been synthesized using the described Mannich-type reaction as the key step.[375,376] Easily removable *N*-protected groups such as Boc, Cbz, Troc (Cl_3CCH_2OCO), and Teoc ($TMSCH_2CH_2OCO$) were bonded to the α-imino ester, and next, their behavior was studied in the Mannich-type addition, with the *N*-Boc and *N*-Cbz-α-imino esters being the most applicable to this reaction. The catalyst was formed by diamine **414** (Ar = 2-MeO-C_6H_4, 10 mol %) and $Cu(OTf)_2$, giving sensibly lower ee's of **443** than the previous reaction (Scheme 73, eq b). The easy deprotection facilitated the synthesis of the enantiomerically enriched biologically active α-AAs **444** and the kynurenine 3-hydroxylase inhibitors **435** (Scheme 71) and FCE28833 **445** (Scheme 73, eq b).[377] The same authors essayed this reaction employing α-hydrazono esters **416** and silyl enol ethers **431** using the diamine **414** (Ar = Ph, 10 mol %) (Scheme 64) as chiral ligand together with ZnF_2 (50 mol %) in aqueous media (THF/H_2O) at 0 °C. The results of compound **440** were not improved (up to 91% ee), and the biologically active product **441** was obtained as well but only with a 90% ee.[378]

However, chiral zinc complexes, generated from different chiral diamines **414** and zinc fluoride, were the appropriate catalysts for the Mannich-type reaction between α-hydrazido ester **416** and the silyl enol ethers **431** to afford enantioselectively the α-AA derivative **446** in very good yield and very high enantioselection (Scheme 74).[379] The diastereoselectivity was also excellent when tetrasubstituted silyl enol ethers were employed as nucleophiles, obtaining the *syn*-stereoisomer as the major compound (R^2 = H). The reaction was performed in water, and a cationic surfactant or triflic acid, as additive, was effective in some particular examples

Scheme 74



Scheme 75

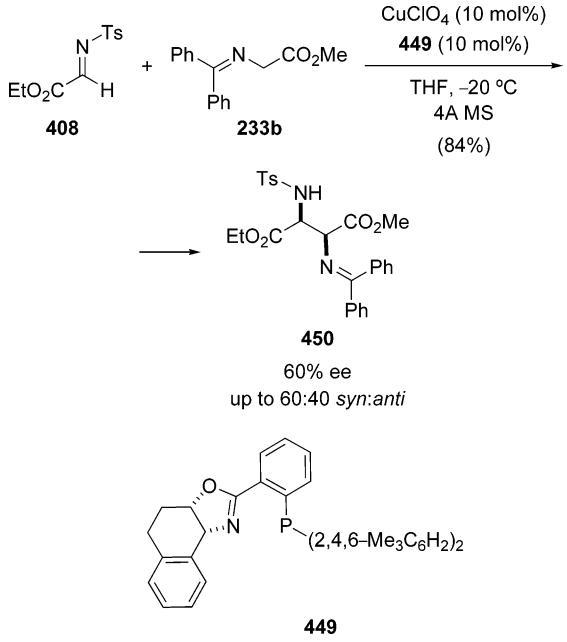


in order to accelerate the reaction (Scheme 74). On the basis of the X-ray analysis, the asymmetric environment of the two phenyl groups was transferred to the benzylic residues attached to each nitrogen atom. The stereospecificity of this reaction demonstrated the importance of the geometry of the enolate, following this rule: the *Z*-*O*-silyl enol ether gave *syn*-adducts **446** as the major reaction products, while the *E*-*O*-silyl enol ether afforded mainly the *anti*-stereoisomer **446**.[358]

The use of enamides as nucleophiles, instead of the enol ethers **431**, was also reported. Several α-imino esters **442** were evaluated in the presence of enamides **447**, employing $Cu(OTf)_2$ (10 mol %) and ligand **414** (Ar = 1-naphthyl, 10 mol %). The enantioselectivity achieved for compounds **448** was quite high (up to 94% ee), and the *syn*-diastereomers were the most abundant products when trisubstituted enamine (R^3 = Me) was employed as nucleophile (Scheme 75).[380] These functionalized structures **448** are also very versatile chiral building blocks for the synthesis of natural products, drugs, and ligands.

Jørgensen's group reported the Mannich-type reaction of compounds **408** with glycine Schiff base **233b** in the presence of the **449**−[Cu] chiral complex. The yield of the new compounds **450** was good, but the diastereo- and enantioselection were moderate (60:40 *syn*/*anti* and 60% ee, respectively) (Scheme 76).[381] The main interest of this molecule **450** is the synthesis of optically active bis-α-AA,

Scheme 76

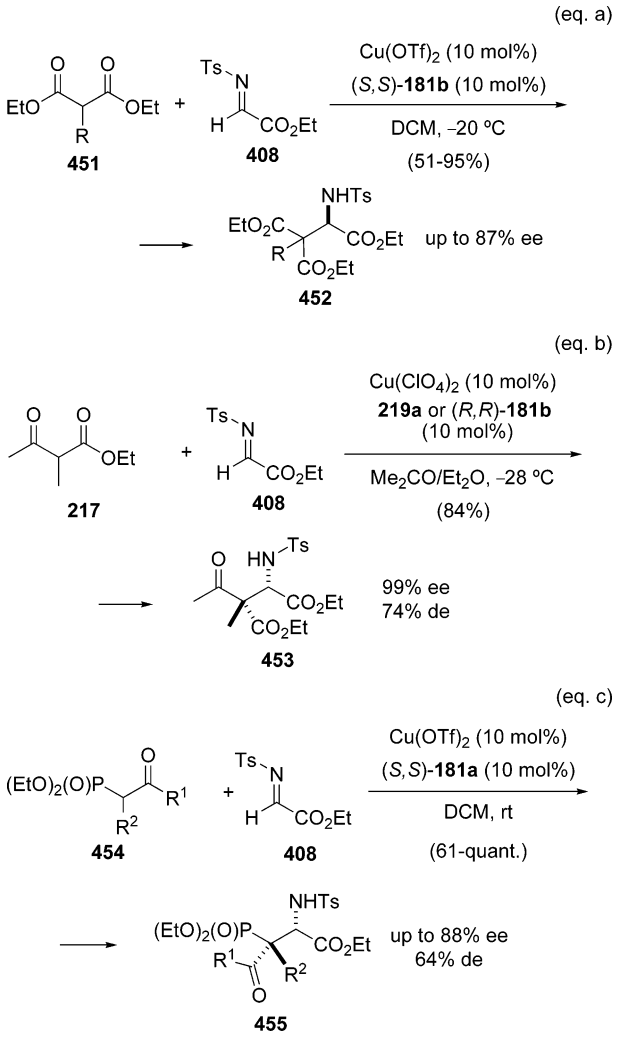


which is not very easily accessible in good ee by using other methodologies.

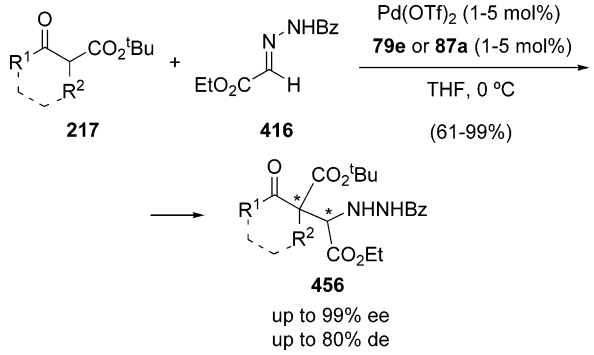
Malonates and β-ketoesters have been tested as carbonucleophiles in the Mannich-type reactions with *N*-tosylimine **408**. A series of articles reported several improvements achieved using a chiral copper catalyst.[382,383] Thus, malonates **451** reacted with **408** in DCM at −20 °C using $Cu(OTf)_2$ and ligand (*S*,*S*)-**181b** (Figure 20), yielding products **452** with good enantiomeric ratios (up to 87% ee) (Scheme 77, eq a).[382] Chiral copper complexes, resulting by a coordination of the metal with chiral oxazoline (*S*,*S*)-**181a** and trisoxazoline **219a** (Scheme 27), have been used in the asymmetric addition of β-ketoesters **217**[217b,382] and β-ketophosphonates **454**,[383] respectively. In both examples, the final products **453** and **455** were obtained as major diastereoisomers and their absolute configuration was determined by X-ray diffraction analysis. In the first example, the C_3-symmetric trisoxazoline **219a** induced a 90% ee as the maximum value of optical purity (Scheme 77, eq b).[217b] Analogous results were obtained for compounds **453** when the reaction was performed with 10 mol % of (*R*,*R*)-**181b** ligand. The novel catalytic enantio- and diastereoselective addition of enolates derived from β-ketophosphonates **454** to activated imino esters **408** was reported, demonstrating that the best catalytic complex was generated from the combination of ligand (*S*,*S*)-**181a** and $Cu(OTf)_2$. The chemical yields of the new optically active phosphonates **455** were moderate to good, and the diastereo- and the enantioselectivity were noticeable (up to 4.6:1 dr and up to 84% ee, respectively) (Scheme 77, eq c).[383]

A highly enantioselective catalytic Mannich-type reaction was optimized from β-ketoesters **217** and α-hydrazido esters **416**. The catalysts employed were based on a palladium complex formed with (*R*)-Binap **87a** (Figure 13), (*R*)-*p*-Tol-Binap **144** (Figure 17), (*R*)-Segphos **79e**, and (*R*)-dm-Segphos **79f** (Figure 13), and the reaction was carried out in THF as solvent at 0 °C, with the **79e** and **87a** ligands being the most efficient ones for this purpose (Scheme 78). The enantiomeric excesses of the compound **456** were, in general, very high (up to 99%) and the diastereoselection was as good as the previous example (up to 80 de). In this

Scheme 77



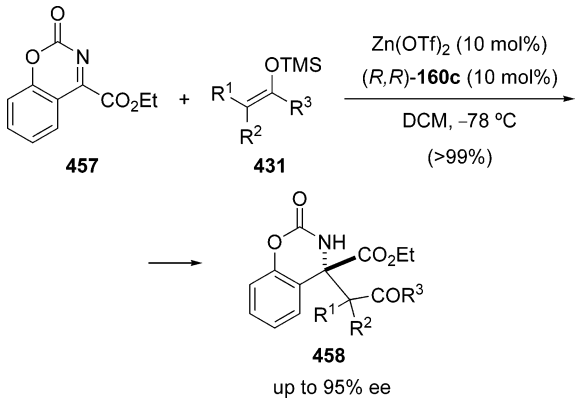
Scheme 78



transformation, the palladium enolate generated an acidic proton, which would activate the imino group at the same time that the palladium complex would coordinate to the enolate, indicating that a dual activation may occur.[384]

Cyclic ketimines **457** underwent enantioselective alkylations by several silyl enol ethers **431**, affording compounds **458** in excellent chemical yields and very good enantioselectivities (up to 95% ee) (Scheme 79). When R^1 or R^2 is different from hydrogen, the resulting diastereoselectivity is not so noticeable (up to 1:8.3) as those of the preceding reactions involving the imino glyoxylates with an intrinsic protective group anchoring.[385] As a general mechanistic conclusion, based on DFT calculations, the simultaneous coordina-

Scheme 79



tion of the imino group and the enolate can account for the facial selectivity as well as the diastereoselectivity observed.

The chiral binaphthoxy samarium complex **459** (Figure 34) was employed (15 mol %) in these Mannich-type reactions of *N*-aryl glyoxylic imines and ketene vinyl acetal, obtaining modest ee's (31−80% ee), except in one example, where a 90% ee was achieved upon addition of 0.6 equiv of aniline.[386] In other work, chiral diamine **460** (Figure 34) was introduced as a ligand of copper salts, obtaining, in general, moderate to good enantioselectivities (up to 85% ee) of the adducts generated from *N*-Cbz-α-methoxy glycinates **433** (X = OMe, Z = Cbz) and silyl enol ethers or enamines.[387]

Subjection of glyoxylate imine **461** and hydroxyacetophenones **462** to the optimized reaction conditions with the catalyst prepared by adding diethylzinc onto the chiral ligand **463** gave a high yield of the *β*-hydroxy-α-AA derivative **464** (Scheme 80). The enantioselectivity was excellent in all of the examples reported, and even the *syn*-diastereoselection was also noticeable, giving *syn*/*anti* ratios higher than 20:1. The highest diastereo- and enantioselectivities corresponded to the reactions carried out with **461** (R = Me) independently of the type of aryl group (Ar^1) of the nucleophile **462**.[388] This reaction was focused onto the synthesis of *syn*-*β*-amino alcohols, *syn*-*β*-hydroxy-α-AA derivatives, and α-hydroxy-*β*-AAs.

Organocatalysis has also been successfully implemented in this type of asymmetric reaction. Thus, the alkylation of the glycine Schiff bases in the presence of chiral PTC agents (disclosed in section 4.1) showed that while activated alkyl halides are of widespread use, there are much fewer reports on the use of aldehydes or carbonyl compounds such as electrophiles. Scarcer still is the use of α-imino esters as electrophiles, and just one example has been reported by Maruoka's group.[389] Chiral spiranic ammonium salts (*R*,*R*)-**312e**,**h**,**i** (Figure 27) were also essayed in the Mannich-type reactions between glycinate Schiff's base **233c** and α-imino ester **430**. Products HCl·**465** were achieved with high enantioselectivity and good diastereoselectivity when using (*R*,*R*)-**312h** as chiral PTC agent at −20 °C and after hydrolysis of the ketimino group (Scheme 81).[389] This free-base bis-amino acid **465** can be considered as a tartaric acid

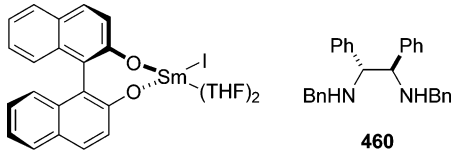
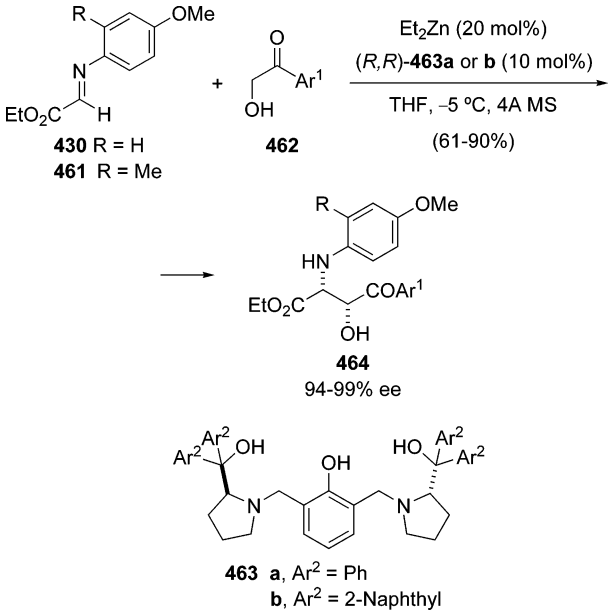
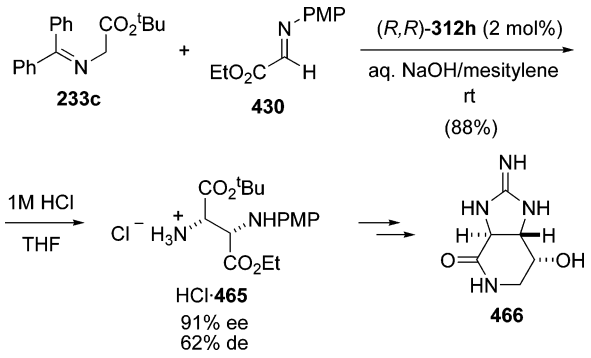


Figure 34. Molecules **459** and **460**.

Scheme 80



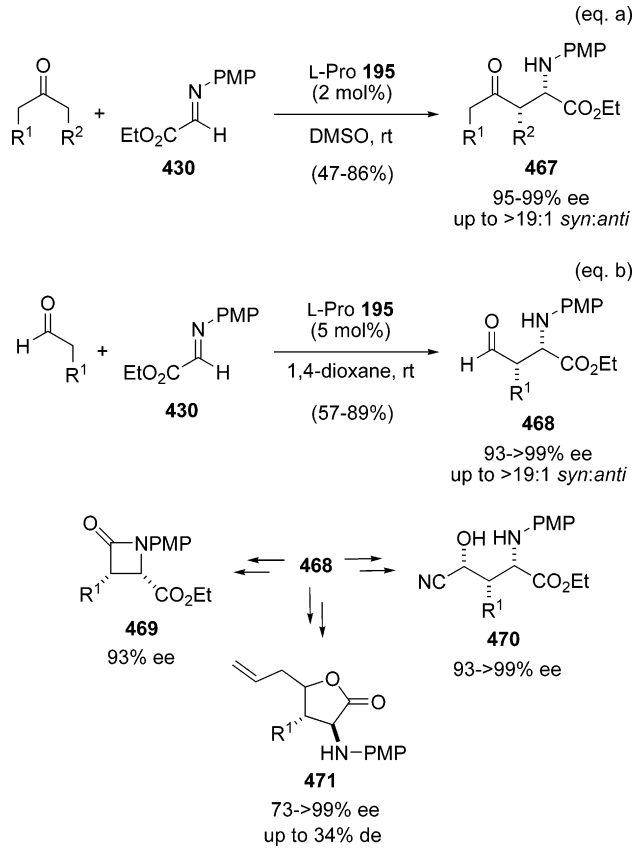
Scheme 81



nitrogen surrogate, which can be an interesting chiral building block in asymmetric synthesis, as, for example, in the enantioselective synthesis of a precursor of streptolidine lactam **466**. This cyclic amide constitutes the core structure of streptothricine antibiotics.

However, reactions using proline as catalyst, pioneered by List[390] and Barbas,[391] are perhaps the most extensively studied examples of organocatalysis in this category. Thus, L-proline (**195**) catalyzed the Mannich-type reactions of the *N*-PMP-protected α-imino ethyl glyoxylate **430** with ketones, providing functionalized α-AAs in high yield with excellent regio-, diastereo- (up to 19:1 *syn*/*anti* ratio), and enantioselectivities (95 to >99% ee) (Scheme 82, eq a). In this reaction, two adjacent stereogenic centers were created simultaneously, and it can be performed on a gram scale.[392] Analogously, aldehydes were allowed to react with **430** in order to obtain good yields of adducts **468**. As we can observe in eq b of Scheme 82, yields were good and both diastereo- (up to >19:1 *syn*/*anti*) and enantioselections (93 to >99% ee) were excellent. The utility of compounds **467** and **468** as chiral building blocks is fascinating. For example, *β*-lactams **470** could be easily obtained after a two-step synthetic sequence from compounds **468**.[393] *β*-Cyanohydroxymethyl α-AA derivatives **470** could be generated, after a trimethylsilyl cyanation, in enantiomerically pure forms with three contiguous stereogenic centers.[394] The *β*-formyl group of molecules **468** was ready to undergo several transformations such as oxidations or indium-promoted

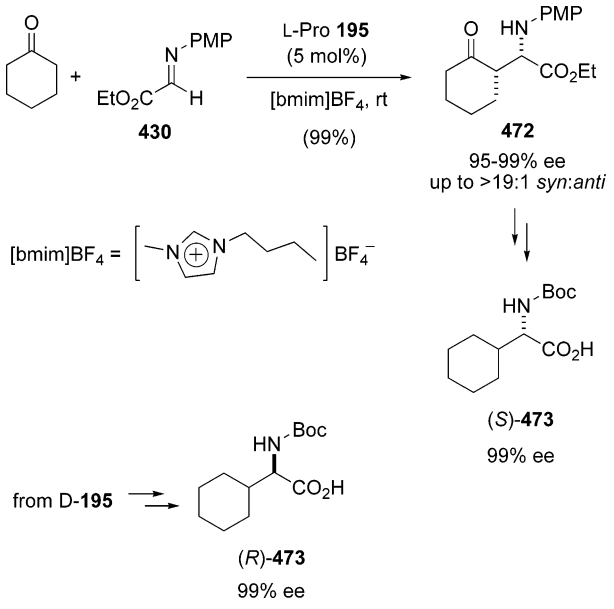
Scheme 82



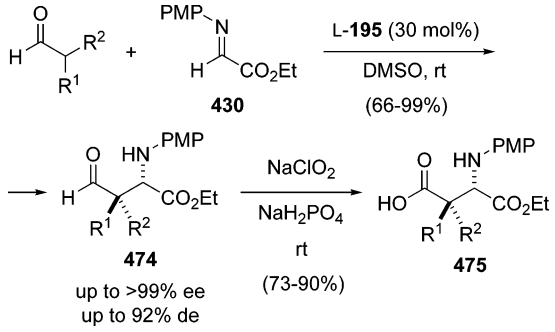
allylation in a one-pot sequence to yield products **469** and **471**, respectively. Despite the fact that the ee of the resulting lactones **471** was very high (93 to >99%), the diastereoselection was only moderate (up to 34% de).[395]

The influence of ionic liquids as solvents in the Mannich-type reaction of *N*-PMP-α-imino ester **430** and aldehydes or ketones was evaluated. The reactions depicted in Scheme 82, employing [bmim]BF_4 as ionic solvent, gave identical yields and diastereo- and enantioselectivities to those reported for the analogous reaction run in DMSO at room temperature. The most differentiating features between both types of reactions were as follows: (a) the product isolation was easier in the reaction performed in the ionic liquid; (b) the catalyst could be recovered from [bmim]BF_4 after extractive workup; (c) the reaction rates were significantly increased in this solvent, ca. 4- to 50-fold.[396] Nevertheless, some limitations on the use of ionic liquids in the proline-catalyzed Mannich-type reaction were detected. Hydroxyacetones **462** could not be used as nucleophile because the dr and ee were quite low, and these reaction conditions could not be extrapolated to (*S*)-2-(methoxymethyl)pyrrolidine (SMP)-catalyzed reactions between α-imino esters and aldehydes.[396] The L-proline **195** catalyzed reaction of cyclohexanone and the α-imino ester **430**, carried out in [bmim]BF_4 as ionic liquid at room temperature, afforded compound **472** in excellent yield (99%) and with extraordinary diastereo- (>90% de) and enantioselectivity (>99% ee). This α-AA derivative **472** was transformed into the *N*-Boc-cyclohexylglycine **473** after a three-step sequence (Scheme 83).[392b] Cyclohexylglycine itself is a constituent of effective inhibitors of the blood coagulation factor X_a and of a doxorubicin conjugate with an oligopeptide of a prostate-specific antigen. Finally, the enantiomer (*R*)-**473** has served as a building block for a serine protease

Scheme 83



Scheme 84

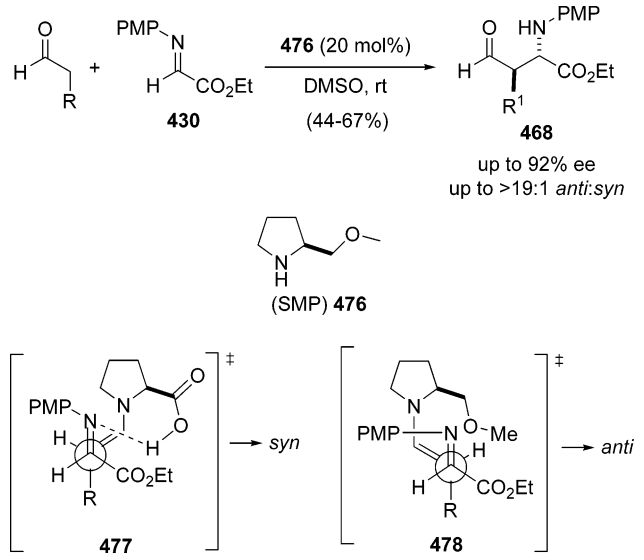


inhibitor used as an anti-inflammatory agent and as an inhibitor of hepatitis C virus.

L-Proline (**185**) also was able to promote the enantioselective addition of α-branched aldehydes to imino esters **430** in good yields using DMSO at room temperature. The adducts **474**, containing quaternary stereogenic centers, were obtained with up to >99% ee for the *syn*-diastereoisomer as the major reaction product. The range of diastereomeric ratios oscillated from 60:40 to 96:4, with the most enriched *syn*-products being transformed into the corresponding L-aspartic acids **475**, after oxidation of the aldehyde group (Scheme 84).[397]

Despite the multiple proline derivatives designed and prepared in order to ameliorate the reaction conditions required when proline (**195**) was used as organocatalyst, very disappointing results of the studied Mannich-type reaction conditions between α-imino esters and enolates have been achieved.[398] The reversal of the relative configuration observed in the Mannich-type reaction between aldehydes and α-imino ester **430** catalyzed by the organocatalyst *O*-methylprolinol (SMP) **476** was noteworthy. The yields were moderate while the *anti*/*syn* ratio was very important (>19:1) and the enantioselectivities were, in general, good but never above the enantioselectivities originated by proline (Scheme 85).[399] In the Mannich transition state, an *E*-configuration was assumed for both the enamine and the imine. In the proline catalyzed reaction (transition-state **477**), the *Si*-face of the imine was attacked by the enanmine's *Si*-face with a potential hydrogen bond from proline carboxylate

Scheme 85



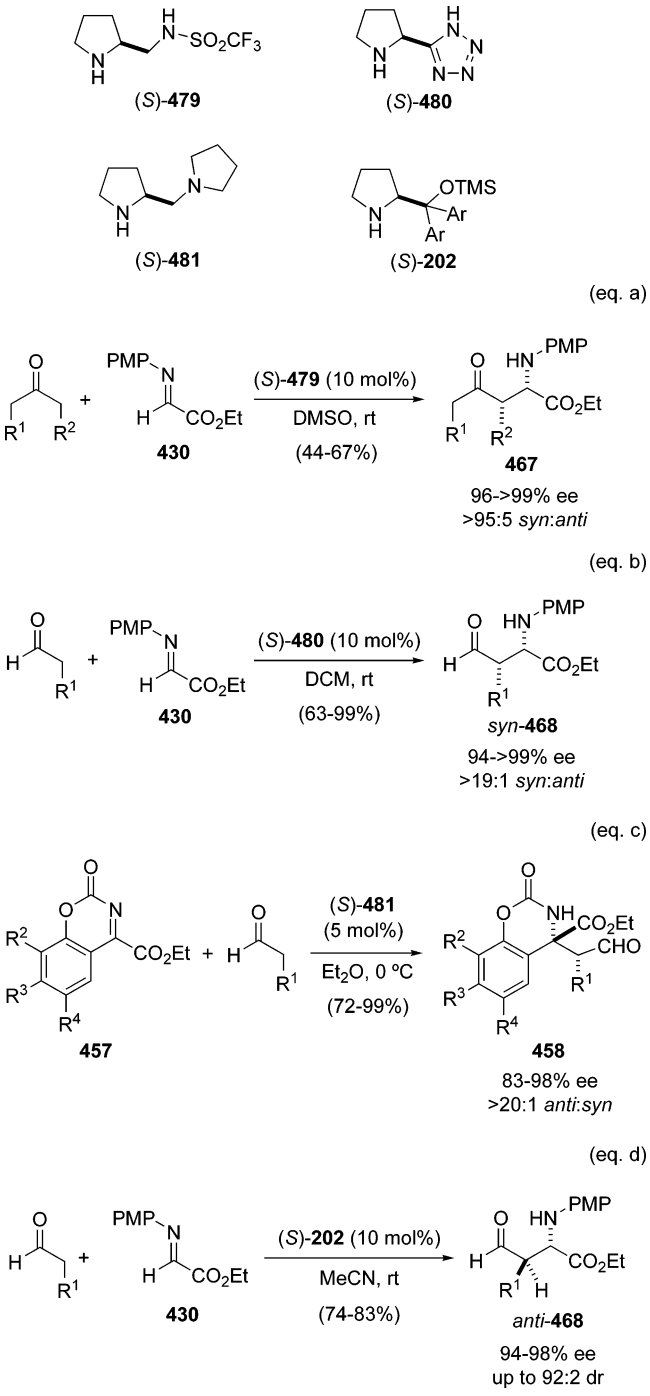
assisting in fixing the relative topicity of the attack and yielding *syn*-product (Scheme 85). Lacking the stereodirecting carboxylate of the proline, the topicity of the SMP-catalyzed reaction the showed that the *Si*-face of the imine was selectively attacked by the *Re*-face of the enamine drawing the ethereal oxygen donor to the imine nitrogen (as occurred in transition state **478**), which, if protonated, may provide for a favorable Coulombic interaction (Scheme 85).[399]

Sulfonamide **479**,[400] the more soluble tetrazole **480**,[401] bispyrrolidine **481**,[402] and prolinol derivative **202**[209b] were essayed in Mannich-type reactions of α-imino esters with aldehydes or ketones in very high chemical yields and excellent both diastereo- and enantioselectivities (Scheme 86). While proline derivatives **479** and **480** gave almost total *syn*-diastereoselection according to the relative positions of the R^2 and NPMP groups of **467** and **468** (Scheme 86, eqs a and b), chiral pyrrolidines **481** and **202** gave the opposite total *anti*-diastereoisomers, **458** and **468**, respectively (Scheme 86, eqs c and d). In the last example, the effect of this crowded side of the catalyst caused an increment in the enantiomeric purity as well as in the diastereomeric ratios of compounds **468** (Scheme 86, eq d). Although these compounds **468** are direct precursors of α-AA derivatives (see above), on this occasion, the corresponding transformation was not reported.[209b]

The highly enantioselective and diastereoselective Mannich-type reaction of α-substituted cyanoacetates **190** was reported using the commercially available chiral amine $(DHQD)_2Pyr$ **483**. An important advantage of this catalytic Mannich-type process is the use of *N*-Boc-protected imines **482**, generated *in situ* by dehydrobromination of the *N*-Boc-protected α-bromoglycine esters. Products **484** were obtained in excellent yields, high diastereoselectivity (up to 98:2 dr), and very good enantioselections (up to 98% ee) (Scheme 87), and they were further transformed into the free amino esters **485** after a selective removal of the Boc-group while the cyano group remained unaltered. Very interesting solvent and structural effects were demonstrated to be crucial for the final stereoselectivity, with the best results being found when DCM was employed as solvent.[403]

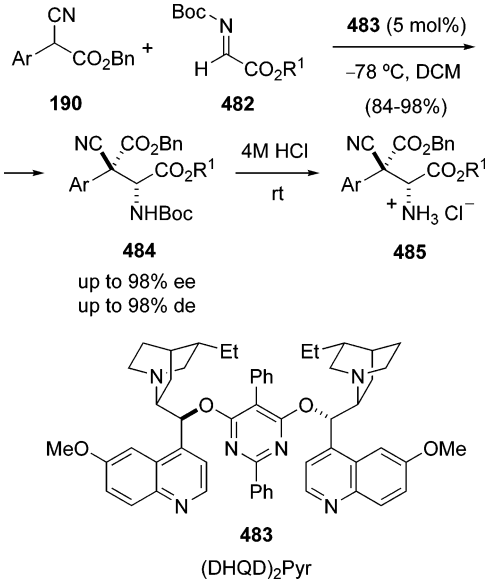
Nitro-Mannich reactions are equally attractive transformations taking advantage of the high acidity of the enolizable nitroalkanes. A heterogeneous asymmetric process catalyzed

Scheme 86

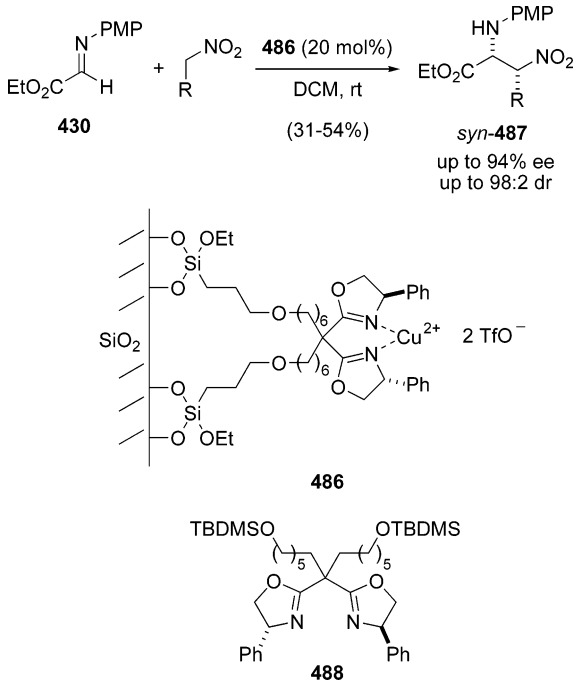


by a bisoxazoline grafted on mesoporous silica **486** has been constructed with the aim of obtaining enantiomerically enriched β-nitro-α-amino esters **487** from nitroalkanes and imines **430**.[404] The enantiomeric excesses were high, but the chemical yields were moderated to low under these heterogeneous conditions. Alternatively, the chiral ligand **488**−[Cu] complex was tested as catalyst for increasing the chemical yields, but it achieved reaction in only one example (R = Et). Moreover, neither enantioselectivity nor diastereoselectivity were improved with respect to the results obtained when catalyst **486** was employed. As an advantage, the chiral system **486** could be recovered and reused five times without any significant loss of reactivity and asymmetric induction (Scheme 88).

Scheme 87

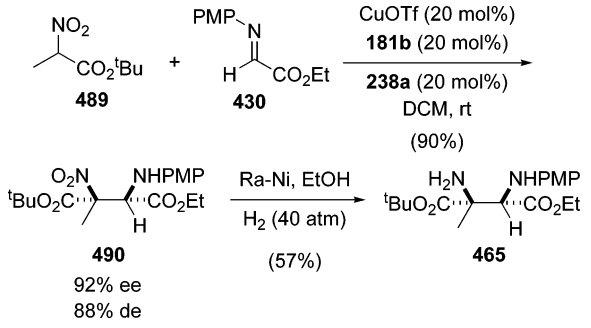


Scheme 88

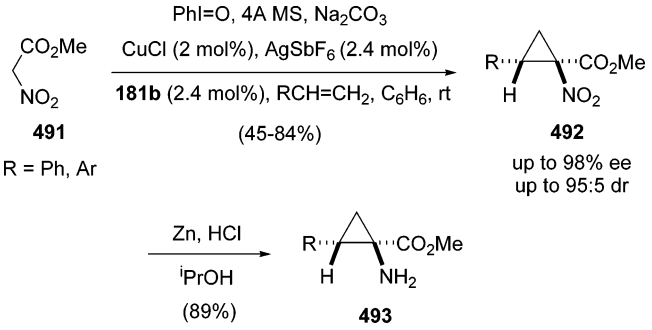


A novel methodology, based on a molecular recognition−dual activation performed by the chiral base quinine **238a** (Figure 22) and (*R*)-Ph-Box **181b** (Figure 20)/Cu(OTf)$_2$ as chiral Lewis acid complex, has been employed in the aza-Henry reaction of α-nitropropanoic esters **489** with the imino ester **430** (Scheme 89).[405] Quinine **238a** afforded the best results of the product **490** rather than other *Cinchona* and *Cinchona*-derived alkaloids, and the ligand **181b** was the most efficient from a series of bis-oxazolidine and bis-pyridine ligands. The matched combination gave product **490** with 98% ee and 88% de in DCM at room temperature. The resulting nitroamine **490** could be easily transformed, by hydrogenation with Ra−Ni under 40 atm of hydrogen pressure, into the corresponding diamine **465**, which is a α,α-bisamino acid derivative with a promising biochemical potential, and as was mentioned before, this type of α-AA is very difficult to obtain by other routes.

Scheme 89



Scheme 90

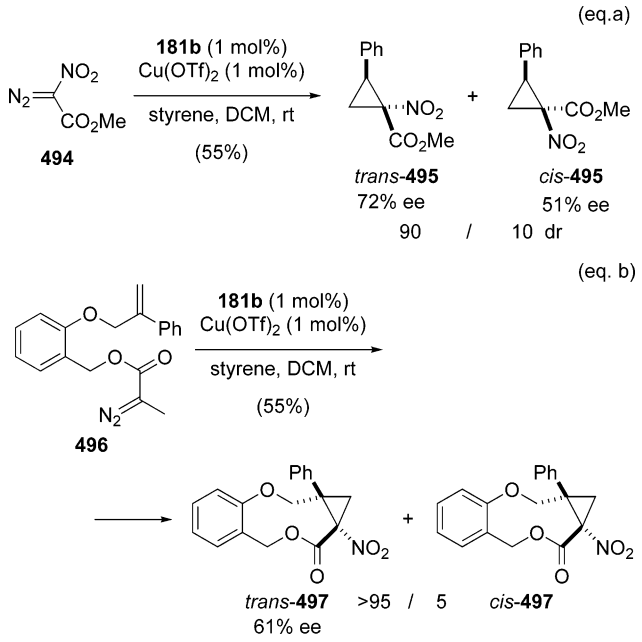


4.3. Cyclopropanations

The enantioselective cyclopropanation have been reviewed, demonstrating the high efficiency of, particularly, copper and zinc chiral complexes.[406,407] The straightforward employment of a catalytic enantioselective cyclopropanation for the synthesis of α-AA derivatives would require the presence of α,*β*-DAAs **1** or α-imino esters. To the best of our knowledge, the cyclopropanation of DAA derivatives was achieved by diastereoselective addition of chiral sulfoxonium and sulfonium ylides, and α-imino esters hardly react with α-alkoxycarbonyl carbenes.[3n,p,s,t,160] However, an additional strategy consisting of the metal-catalyzed asymmetric cyclopropanation reaction of α-nitrogenated α-alkoxycarbonyl carbenes to alkenes (Scheme 1, eq k) emerged as a valuable route to achieve α-amino cyclopropanecarboxylic acids (ACCs). These fascinating α-AAs are interesting because they affect the chemical and biological properties in peptides through significant conformational restrictions in the α-AA residues. In addition, some naturally occurring ACCs exhibit crucial roles in plant growth and fruit ripeness.[3h,188]

Very recently, the enantioselective synthesis of α-amino cyclopropanecarboxylic acids has been achieved using a different approach based on the generation of the corresponding carbene from methyl nitroacetate **491** and PhI═O instead of the dangerous diazo compounds.[408] This study was initiated using styrene, PhI═O, molecular sieves to scavenge water, and the complex of the commercially available chiral bisoxazoline Ph-Box **181b** (Figure 20) and Cu(MeCN)$_4$PF$_6$ as catalyst. The optimized reaction conditions are shown in Scheme 90, demonstrating that the effect of the catalyst counterion on the reactivity and enantioselection is very important; in fact, the addition of the hexafluoroantimonate (SbF_6^-) was crucial and necessary to obtain excellent enantioselections in the generation of cyclopropanes **492**. The elevated dr's and ee's obtained through this efficient and practical method ensure its wide application in synthesis. In an additional step, the nitro group was reduced by zinc-metal in acidic media, giving the α-amino ester **493**, or even it

Scheme 91



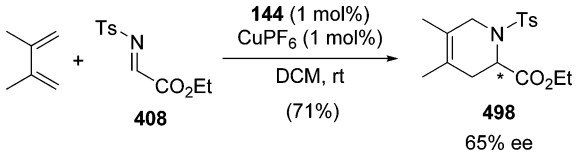
could be transformed into the chiral amine by a reductive decarboxylation reaction.[409] This α-amino ester is a direct precursor of ACCs, which are very important substances in synthetic organic chemistry and in nature, possessing fascinating and numerous biological applications.[3n,p,s,t,410]

Previously to this efficient method, the same group reported the asymmetric inter- and intramolecular cyclopropanation using α-nitro-α-diazocarbonyl substrates **494**. In this reaction, promoted by rhodium(II) salts, several chiral ligands were surveyed. Thus, structures derived from L-proline **195**, phenylalanine, *β*-lactams, and a phosphate derived from chiral (*R*)-Binol were coordinated to rhodium(II) salts to afford chiral complexes, which did not give more than 17% ee of the *trans*-cyclopropanes **495** together with noticeable amounts of the *cis*-**495** isomer.[411] However, in the analogous intermolecular copper-catalyzed cyclopropanation, the combination of Box-ligands **181** (especially Ph-Box **181b**) afforded the better dr and ee of the corresponding cyclopropanes **495** in moderate chemical yields (Scheme 91, eq a). The enantioselection of the intramolecular version of this enantioselective cyclopropanation, catalyzed by chiral rhodium(II) complexes, was even lower (up to 61% ee), but chemical yields and diastereoselectivities in products **497** were significantly higher than those obtained in the intermolecular reaction (Scheme 91, eq b).[411]

4.4. Enantioselective Cycloaddition Reactions

Cycloaddition reactions have fascinated the chemical community for generations. The basic principle dealing with the conservation of the orbital symmetry in concerted reactions is very advantageous because this steric control favors the formation of several stereogenic centers in only one reaction step.[412] Some important syntheses of cyclic α-AA are achieved employing an enantioselective cycloaddition reaction such as the aza-Diels−Alder [4+2] reaction, the most numerous 1,3-dipolar cycloaddition reactions of azomethine ylides [3+2], and formal [2+2] combinations, such as was exemplified in Scheme 1 (eqs l, m, and n, respectively).

Scheme 92



4.4.1. Aza-Diels–Alder Reactions

The Diels−Alder reaction has been widely studied and extensively applied in general organic synthesis,[412−414] and major advances have occurred in the development of stereoselective versions.[413] The aza-Diels−Alder reaction is regarded as one of the most useful reactions available for the synthesis of nitrogen-based heterocyclic ring systems, including the cyclic amino acid family, such as pipecolic acid derivatives and bicyclic α-AAs, which incorporates a carbon−nitrogen bond in either the diene or the dienophile (Scheme 1, eq l).[414] Despite the stability of 2-azadienes and their utility in heterocyclic synthesis, the α-imino esters are preferred as dienophiles in the aza-Diels−Alder reaction to obtain enantioselectively cyclic α-AA derivatives.

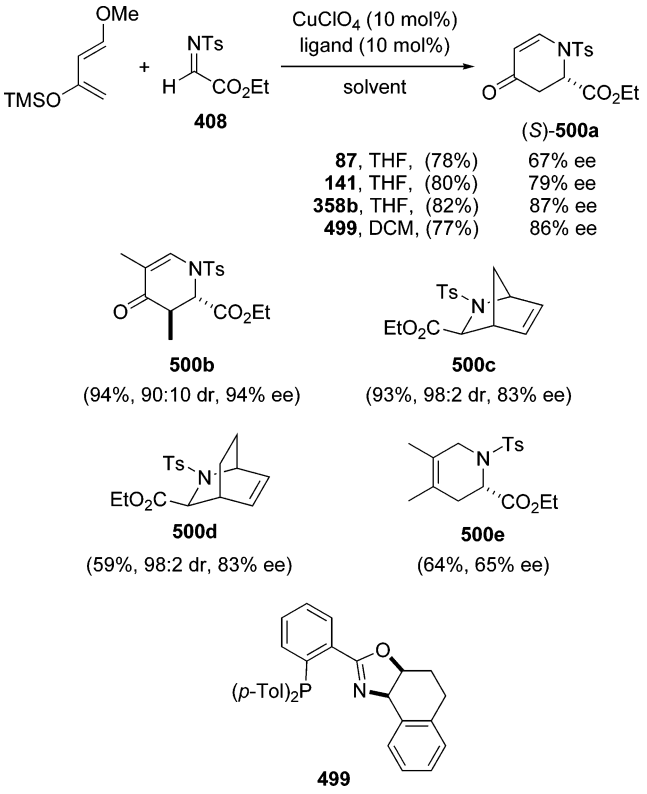
During the study of the ene reaction between *N*-tosyl-α-imino ester **408** and 2,3-dimethylbuta-1,3-diene in the presence of $CuPF_6$ (10 mol %) and equal amounts of (*R*)-*p*-Tol-Binap **144** (Figure 17), the cycloaddition product **498** was unexpectedly obtained as the major compound.[341] Under the reaction conditions depicted in Scheme 92, the enantioselectivity was not too high (65% ee) but encouraged the authors to improve this methodology.

It was found that *N*-tosyl-α-imino ester **408** reacted with Danishefsky's diene in the presence of substoichiometric amounts of chiral Lewis acids to afford the aza-Diels−Alder adduct **500** in an enantioselective manner. It was revealed that $CuClO_4$, in combination with ligand *p*-Tol-Binap **144** or with phosphinooxazoline ligands such as **358b** (Figure 30) and **499**, gave the highest enantioselectivity (up to 87% ee).[415] A comprehensive study with other dienes was done, obtaining very high diastereoselectivities and enantioselections for the major diastereoisomers **500b**−**e**, employing *p*-Tol-Binap **144** (Figure 17) as ligand. It was noted that the *exo*-adduct **500** was obtained preferentially under mild reaction conditions (Scheme 93).

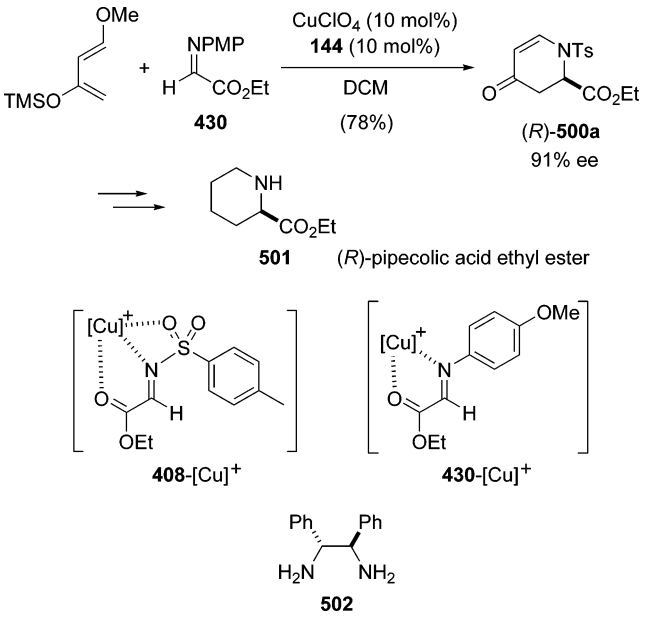
The α-imino ester **430**, bearing a PMP substituent, also reacted with Danishefsky's diene in the presence of 10 mol % of a *p*-Tol-Binap **144**−[Cu] complex to give the corresponding adduct in high yield and very good ee, but with opposite configuration from that reported for **500a** (Scheme 94).[353] This notable change in the enantiodiscrimination course was explained by assuming tridentate and bidentate coordination of the copper atom with *N*-tosyl-imino ester **408** and with the imine **430**, respectively (Scheme 94). This different type of coordination to the metal center could transform the metallic aggregate ready to react with the diene, favoring one of the two different approaches according to the molecular modeling studies and X-ray diffraction analysis. In this particular example, the absolute configuration of compound (*R*)-**500a** was determined by correlating it to the commercially available optically active pipecolic acid ethyl ester **501** using three additional steps.[415]

The synthesis of compound (*R*)-**500a** (Scheme 94) was developed as well using parallel combinatorial methods. In this contribution, ytterbium and copper triflates, magnesium iodide, and iron trichloride have been employed as Lewis acids in the aza-Diels−Alder reaction of **430** and Danishef-

Scheme 93



Scheme 94



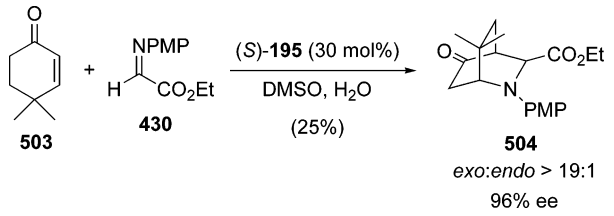
sky's diene. The chiral ligands employed were ^{t}Bu-Box **181a** and (1*S*,2*S*)-1,2-diphenylethylenediamine **502** (Scheme 94), with the last one being the most effective, together with magnesium iodide as Lewis acid. In Table 20, the most important and representative examples of this work are summarized.[416] Lower enantioselectivities (up to 68% ee) than those depicted in this table were observed when stoichiometric chiral Binol−Zn complexes were used in the reaction shown in Scheme 94.[417]

(*S*)-Proline **195** also catalyzed the reaction of **503** with imino ester **430**, furnishing the valuable bicyclic α-AA derivative **504**, which was isolated in low yield but with excellent enantioselection (96% ee) (Scheme 95). According to the intermediates isolated from the crude reaction, this global aza-Diels−Alder process was presumably obtained by a sequential domino Mannich/Michael-type addition process with excellent chemo-, regio-, enantio-, and diastereoselectivities. The proposed transition state and the chemical course of the reaction, favoring the *exo*-product **504**, represented a valuable alternative to the conventional Diels−Alder reaction, where the *endo*-adduct is, generally, the expected major reaction product.[418]

Table 20. Aza-Diels−Alder Reaction of 430 and Danishefsky's Diene Mediated by Chiral Ligand−[Metal] Complexes

				product (*R*)-**500a**	
Lewis acid	ligand	additive	solvent	yield (%)	ee (%)
MgI_2	**502**	2,6-lutidine	MeCN	64	97
$Y(OTf)_3$	**502**	2,6-lutidine	PhMe	60	87
$Cu(OTf)_2$	**502**	none	MeCN	58	86
$FeCl_3$	**181a**	4 Å MS	DCM	67	92

Scheme 95

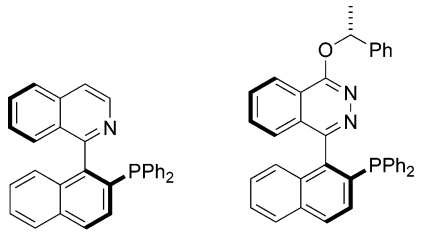


2-Benzyloxycarbonylazirines are constrained−very reactive−α-imino esters, which were allowed to react with cyclopentadiene in the presence of stoichiometric amounts of chiral Lewis acids, affording, at very low temperatures (−60 °C), poor yields (up to 41%) and modest enantioselectivities (up to 52% ee) of the corresponding cycloadducts.[419]

4.4.2. 1,3-Dipolar Cycloaddition Reactions of Metallo-azomethine Ylides

The 1,3-dipolar cycloaddition reaction of azomethine ylides and electrophilic alkenes (Scheme 1, eq m) allows the preparation of the polysubstituted proline derivatives diastereoselectively.[420] A very easy and practical route to generate the azomethine ylides is by the treatment of Schiff bases **233** with a Lewis acid and a base, both in substoichiometric amounts. The benefits of the *in situ* preparation of these metallo-dipoles and the generation of four stereogenic centers simultaneously make this reaction much more attractive. The asymmetric version of this reaction involving the use of a chiral Lewis acid or even a chiral base in substoichiometric amounts is currently a very exciting research area,[420a] which started with the contribution of Zhang's group in 2002, although stoichiometric chiral Lewis acids were successfully employed by Grigg's group 10 years ago. In a recent revision, chiral ligands **79e**, **87a**, (*R*,*R*)-**346**, **347b** (Figure 30), (*R*)-Ph-Box **181b** (Figure 20), (*S*)-Quinap **505**, and *O*-(*S*)-Pinap **506** (Figure 35) proved to be very efficient ligands using silver or copper salts (Table 21) for the enantioselective 1,3-dipolar cycloaddition reaction of azomethine ylides with electron-poor alkenes.

Apart from these enantioselective 1,3-dipolar cycloaddition reactions, other chiral ligands have been described with the aim of unveiling the most versatile and widely used combination in asymmetric synthesis (Figure 36). Phox-ligands **507** were used for the screening process of the

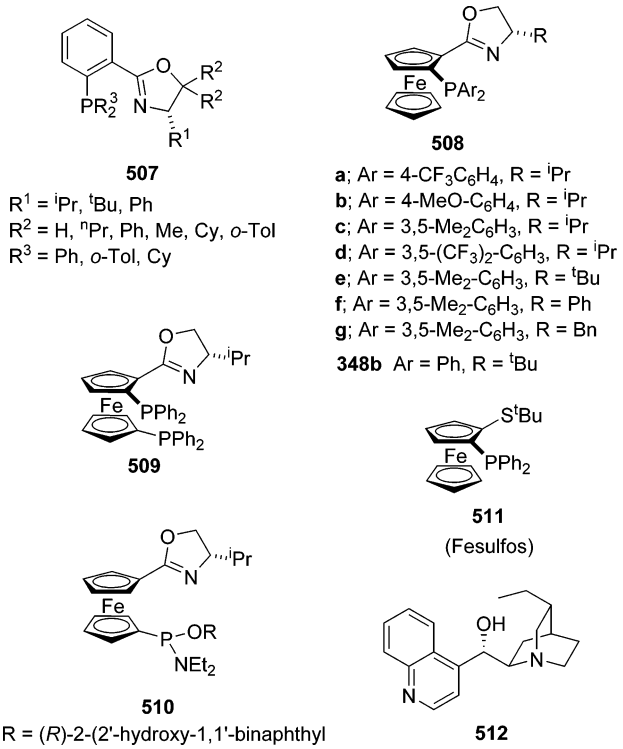


505 (*S*)-Quinap **506** *O*-(*S*)-Pinap

Figure 35. Ligands **505** and **506**.

intermolecular 1,3-dipolar cycloaddition reaction of the imino ester **233** (R^1 = 1-naphthyl, R^2 = H) and methyl acrylate, obtaining the cycloadducts *endo*-**513** with the best *endo*-diastereoselectivity and enantioselectivity (65% ee) when ligand **507h** (R^1 = ^{i}Pr, R^2 = Ph, R^3 = *o*-Tol) was used in the presence of silver acetate (Scheme 96, eq a).[426] However, the intramolecular cycloaddition reaction of **514** employing the same catalytic system was very successful because only one stereoisomer **515** was obtained in 99% ee, giving access to polyfused cyclic structures (Scheme 96, eq b), which are potentially valuable for the construction of the core structures of natural products.[426]

The copper-catalyzed 1,3-dipolar cycloaddition reaction of azomethine ylides derived from **233** employing ligands **345b** (Figure 30) and **508** was reported independently by two groups with some different chemical details. The first report tested the ligands **345b** and **508**−**510** in the cycloaddition between imines **233** and nitroalkenes, obtaining very interesting and different results depending on the chiral ligand employed. The catalytic complex **508a**−[Cu] (10 mol %) afforded, in THF at 0 °C and using KO^{t}Bu as base (10 mol %), excellent *exo*-selectivities and very high to excellent ee's (up to 99%) of the *exo*-**516** cycloadducts (Scheme 97, eq a).[365] Nevertheless, the introduction of an electron-deficient



507
R^1 = ^{i}Pr, ^{t}Bu, Ph
R^2 = H, ^{n}Pr, Ph, Me, Cy, *o*-Tol
R^3 = Ph, *o*-Tol, Cy

508
a; Ar = 4-$CF_3C_6H_4$, R = ^{i}Pr
b; Ar = 4-MeO-C_6H_4, R = ^{i}Pr
c; Ar = 3,5-$Me_2C_6H_3$, R = ^{i}Pr
d; Ar = 3,5-$(CF_3)_2$-C_6H_3, R = ^{i}Pr
e; Ar = 3,5-Me_2-C_6H_3, R = ^{t}Bu
f; Ar = 3,5-Me_2-C_6H_3, R = Ph
g; Ar = 3,5-Me_2-C_6H_3, R = Bn

348b Ar = Ph, R = ^{t}Bu

509

511 (Fesulfos)

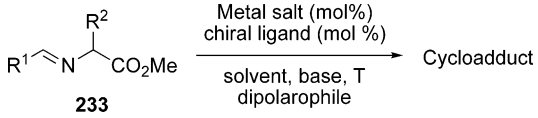
510
R = (*R*)-2-(2'-hydroxy-1,1'-binaphthyl

512

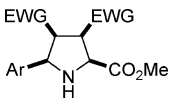
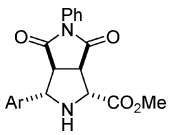
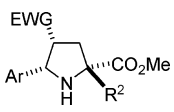
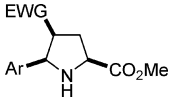
Figure 36. Some efficient chiral ligands used for the catalytic enantioselective 1,3-dipolar cycloaddition reactions of azomethine ylides and alkenes.

aryl group as a substituent on the phosphorus atom [Ar = 3,5-$(CF_3)_2C_6H_3$, **508d**] formed a copper complex which induced very high enantioselection (up to 98%) of the more abundant *endo*-**516**. In this case, the *endo*/*exo* ratio (up to 94:6) was not as high as that reported for the reaction catalyzed by the **508a**−[Cu] complex.[427] This fact demon-

Table 21. Summary of the Already Reviewed Catalytic Enantioselective 1,3-Dipolar Cycloaddition Reactions Involving Metallo-azomethine Ylides

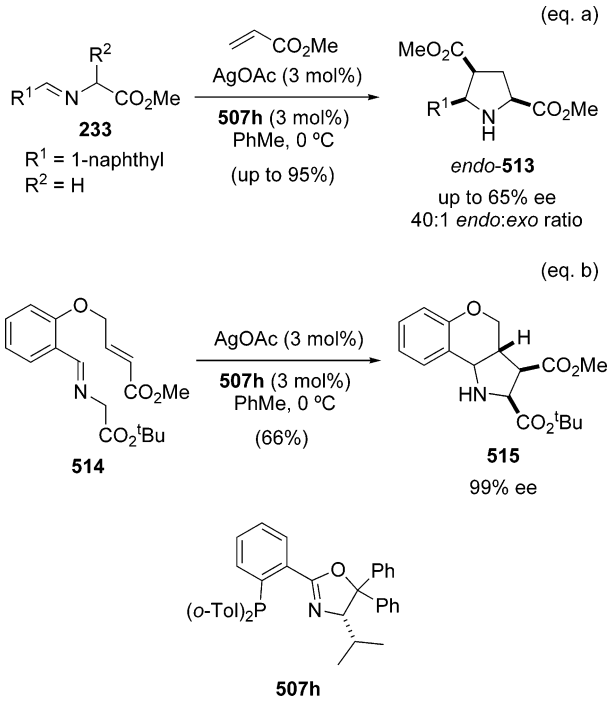


233

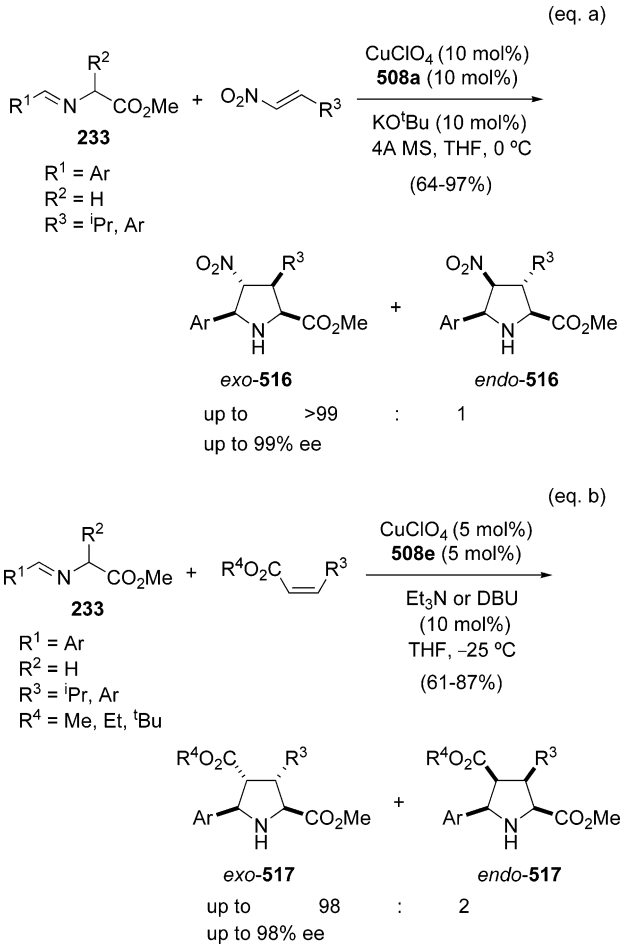
R^1	R^2	metal salt (mol %)	ligand (mol %)	dipolarophile	solvent	base	*T* (°C)	cycloadduct yield[a] (%)	cycloadduct structure	cycloadduct ee (%)	ref
Ar	H	AgOAc (3)	**347b** (3.3)	maleates	MePh	DIEA[b]	0	73−98		60−97	421
Ph	H	$Cu(OTf)_2$ (2)	**79e** (2.2)	NPM[c]	DCM	Et_3N	−40	78[d]		72	422
4-MeO-C_6H_4	H/alkyl	$Cu(OTf)_2$ (2)	**87a** (2.2)	NPM[c]	DCM	Et_3N	−40	83[e]		87	422
Ar	H/alkyl	AgOAc (3)	**505** (3)	acrylates	THF	DIEA[b]	−20 to −45	92−98		80−96	423
Ar	H	AgOAc (3)	**506** (3)	acrylates	THF	DIEA[b]	−40	94		95	424
Ar	H	AgOAc (3)	**181b** (3)	acrylates	THF	Et_3N	−20	84−95		78−91	425

[a] Isolated yields. [b] DIEA = diisopropylethylamine. [c] NPM = *N*-phenylmaleimide. [d] 89:11 *exo*/*endo* ratio. [e] >95:<5 *exo*/*endo* ratio.

Scheme 96

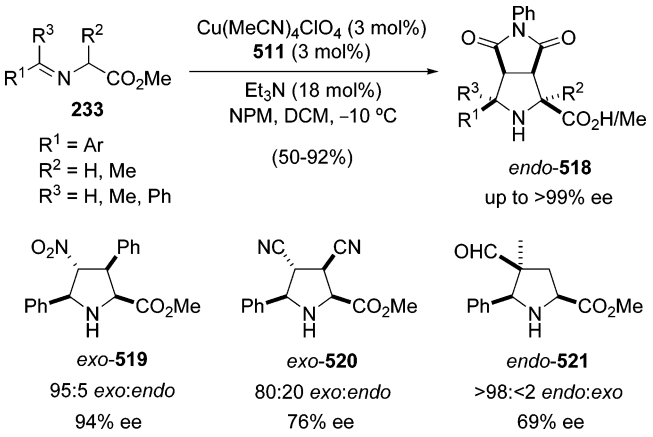


Scheme 97



strated the importance of modifying the electronic properties of the ligand in order to invert the diastereo- or the enantioselectivities of the same process (fine-tuning catalyst). Computational studies of the catalytic chiral copper complex were performed assuming that a possible electronic interaction between the nitro group and the copper complex could be responsible for this reversal diastereoselection.[427] The second contribution involving ligands **508** studied a series of chelating structures in the enantioselective 1,3-dipolar cycloaddition reaction of acrylates or maleates with Schiff bases **233**. As occurred in the majority of the examples catalyzed by copper species, the *exo*-adducts were the more abundant diastereoisomers. Here, chiral catalyst **508**−[Cu] induced, at −20 °C in THF, a very good enantioselectivity (up to 98% ee) of the corresponding *exo*-**517** cycloadduct (up to 98:2, *exo*/*endo* ratio) in good chemical yields (Scheme 97, eq b).[428]

Scheme 98

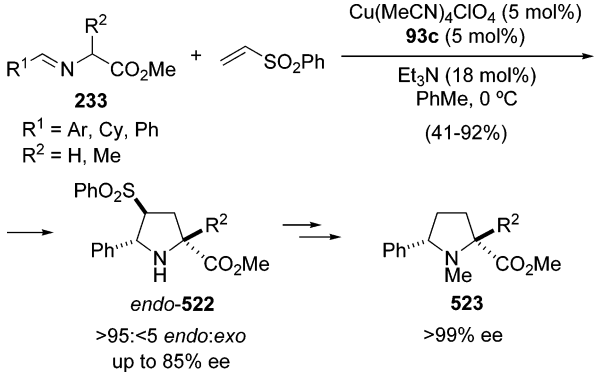


The total inversion of the diastereoselectivity, to the detriment of the *exo*-cycloadducts, could be directed by using silver salts; thus, the *endo*-**517** cycloadduct was obtained (>98% de) with high enantioselection (up to 98% ee) when a catalyst formed from 3 mol % of **508g** and AgOAc was employed in diethyl ether at −25 °C in the absence of an extra base. The influence of the electronic properties of the phosphorus substituents in ligands **508** was also detected and further studied in the improvement of the enantioselection of the title transformation.[429]

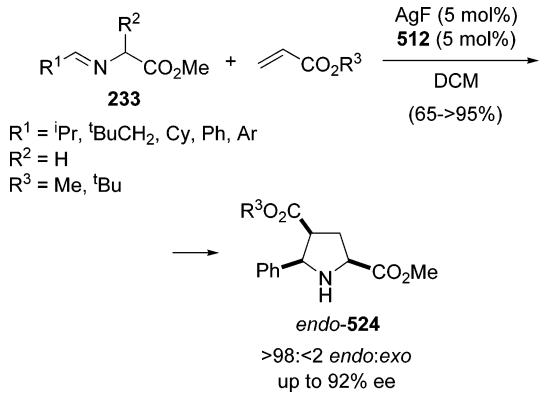
The Fesulphos **511**−[Cu(I)] (Figure 36) catalytic system shows excellent performance in the enantioselective 1,3-dipolar cycloaddition of azomethine ylides derived from **233** with *N*-phenylmaleimide (NMP), affording the *endo*-adduct as the unique reaction product *endo*-**518** and with very high enantioselectivities (Scheme 98).[430] This is a unique example catalyzed by a copper complex that exhibited an anomalous behavior; that means, the *endo*-adduct was isolated, in some occasions, rather than the expected *exo*-diastereoisomer, but compounds *exo*-**519** and *exo*-**520**, derived from β-nitrostyrene, were obtained, presumably, due to a different coordination of the electron-rich nitro and cyano groups to the metal center.[430] In the reaction run with methacroleine, the *endo*-adduct **521,** incorporating a quaternary stereogenic center, was isolated in very good yield but lower enantioselection.

The same group also reported a very similar reaction using vinylic sulfones as dipolarophiles in a copper-mediated 1,3-dipolar cycloaddition reaction. From a large collection of phosphorus ligands, the total *exo*-selectivity and highest ee were gained by employing a Taniaphos ligand (Figure 14) **93c**−[Cu] complex.[431] All of the substituents in both dipole and dipolarophile, solvents, and bases were evaluated, with the best results being obtained for the reaction conditions described in Scheme 99, introducing phenyl vinyl sulfone as a 2π-electron component. A direct application of this reaction was the transformation of the *endo*-prolines **522** into

Scheme 99



Scheme 100



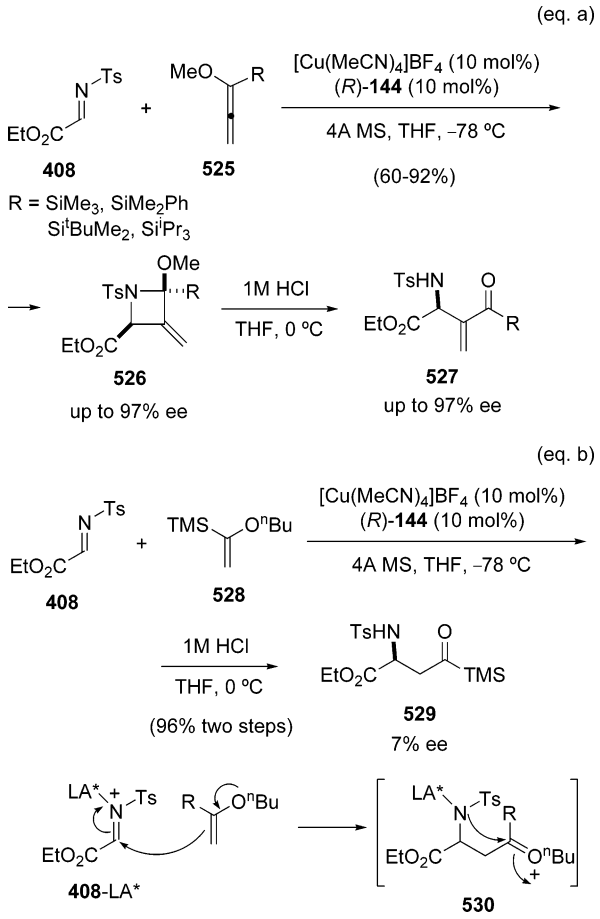
the enantiomerically pure pyrrolidines **523**, where the vinyl sulfone acted as a synthetic equivalent of ethylene, a type of unactivated olefin unsuitable for the reaction with azomethine ylides.[431]

Other different approaches for carrying out the enantioselective reaction were the addition of a chiral base in a substoichiometric amount. The reaction between *N*-alkylidene glycine esters **233** and *tert*-butyl acrylate catalyzed by silver fluoride and the commercially available chiral base hydrocinchonine **512** (Figure 36) proceeded with high *endo*-diastereoselectivity and moderate to good enantioselectivity (up to 73% ee and up to 92% ee after recrystallization). Many cinchonine and cinchonidine derivatives, as well as silver salts, were essayed, obtaining better conversions and more reproducible results when employing silver fluoride and the highest ee in the reactions performed with chiral base **512** (Scheme 100).[432] It is worthy to note that the use of less stable aliphatic imino esters **233** (R^1 = Cy, ^{i}Pr, and ^{t}BuCH$_2$) gave good yields and moderate enantioselectivities when it is very well-known that these substrates afforded very large amounts of products derived from the Michael-type addition reaction and poor yields of the expected cycloadducts. The whole number of the proline derivatives described in this section never was transformed into the corresponding functionalized α-AAs despite the extraordinary importance of them in many scientific areas.

4.4.3. [2+2] Cycloadditions

The [2+2] cycloaddition reactions involving alkenes or allenes and α-imino esters offer the possibility to obtain a very interesting family of α-AA derivatives named 2-azetidinecarboxylic acid derivatives (Scheme 1, eq n). These molecules can even be transformed in more functionalized structures such as allylic acids, oxoaminoacids, etc. For this purpose, the forbidden thermal [2+2] cycloaddition reaction, exclusively allowed when ketenes or allenes are involved in this electrocyclic reaction, can be circumvented employing a formal [2+2] reaction based on a sequential domino-Michael-type−Dieckmann-type reaction[433] or a Michael-type aldol reaction,[434] but, to date, only diastereoselective processes have been reported. However, a Cu(I) catalyzed enantioselective [2+2] cycloaddition of 1-methoxyallenylsilane **525** with *N*-tosyl α-imino ester **408** has been described in the literature. The catalyst employed was formed from a (*R*)-*p*-Tol-Binap (Figure 17) **144**−[Cu] complex (10 mol %), and the reaction was performed in THF at −78 °C and using 4 Å MS. The process occurred with very high conversions and chemical yields, affording chiral azetidines **526** (up to 97% ee). These α-AA derivatives **526** underwent the ring opening of the azetidine without any loss of the initial optical purity, furnishing chiral α-amino esters **527** with very interesting functionality at the *β*-carbon atom (Scheme 101, eq a).[435] Unfortunately, the reaction of 1-butoxyvinylsilane **528** and **408** gave, after acidic hydrolysis, an acylsilyl-*β*-amino ester **529** with a 97% ee and 96% overall yield (Scheme 101, eq b). The generation of the corresponding azetidines can be explained by a probable Lewis acid-promoted Mannich-type addition onto the activated α-imino ester **408**-LA*, followed by the intramolecular attack of the charged nitrogen atom to the oxonium moiety in intermediate **530** (Scheme 101).[435]

Scheme 101



As a partial conclusion of this section, it is obvious that the use of PTC conditions is more suitable for the elaboration of whatever α-AA structure, under very mild reaction conditions. Here, the recuperation of the catalyst is a rather well studied and successfully resolved aspect. The processes

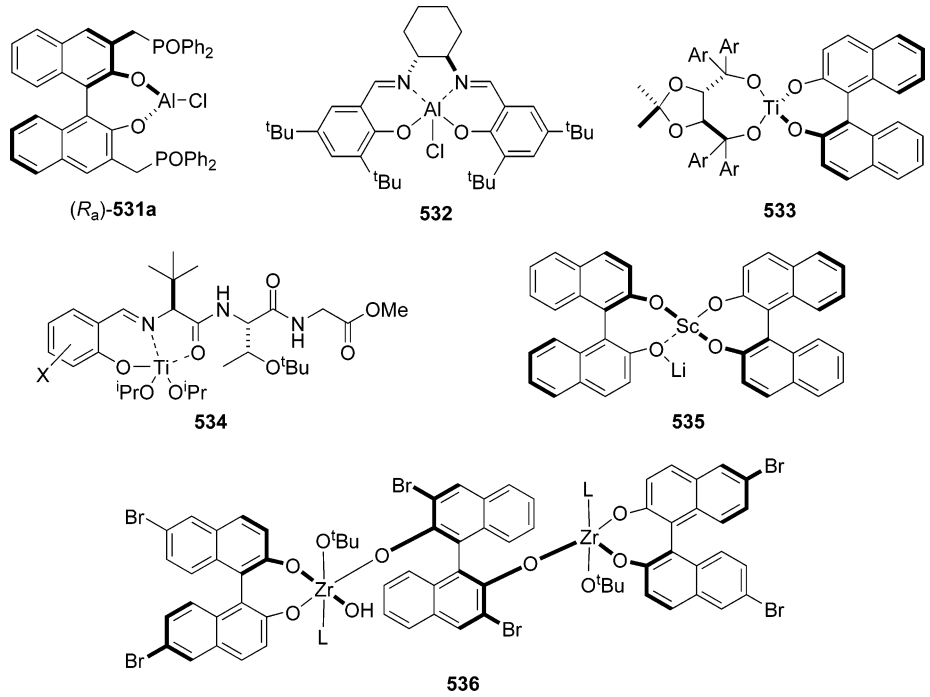


Figure 37. Chiral metal complexes used in enantioselective Strecker reactions.

are very enantioselective; they require relatively small amounts of organocatalytic salt, furnishing excellent chemical yields. *Cinchona* derived PTC agents are preferred because they are easily modified through standard chemical protocols, rather than the spiroquaternary ammonium salts, although impressive results have been published using them. The other described routes for the enantioselective introduction of the α-side chain are also valuable to obtain very specific α-AA structures, but especially relevant is the catalytic enantioselective 1,3-dipolar cycloaddition reaction, which allows the stereocontrolled generation of polysubstituted prolines.

5. Enantioselective Introduction of the Carboxy Group

The enantioselective cyanide addition onto imines and analogous syntheses constitute an elegant way to introduce asymmetrically a masked carboxylic group. The most important example of this strategy is the Strecker reaction, which originally comprises a condensation of an aldehyde, ammonium salt, and a cyanide source, followed by hydrolysis.[2d,3a,160a,b,357b−d,436,437] When using amines instead of ammonia, the previous generation of the imine occurred very rapidly and the reaction was also a success. Another common practice in chemistry is the employment of already generated imines or *N*-substituted imines, which undergo the cyanide addition (Scheme 1, eq o), and in further chemical steps, the nitrile group can be transformed into the corresponding carboxylic acid or ester. Despite the fact that this reaction was reported in 1850, and it is the oldest known synthesis of α-AAs, the first catalytic enantioselective version was not published until 1996 by Lipton's group.[436c]

Similarly, the catalytic enantioselective Reissert-type reaction, first reported by Shibasaki's group in 2000, involving the addition of the cyanide group onto *in situ* generated *N*-acylquinolines or *N*-acylisoquinolines, is considered in this section as a Strecker-modified reaction (Scheme 1, eq o).[436c]

As the cyanide anion is the nucleophile in these two reactions, nitroalkanes in basic media are efficiently added to imines. In an additional step, the carboxylic acid is generated from the nitromethyl group. This reaction, named the nitro-Mannich or aza-Henry reaction (Scheme 1, eq p), can be enantioselectively performed by the intermediacy of chiral catalysts.

5.1. Strecker-Type Reactions

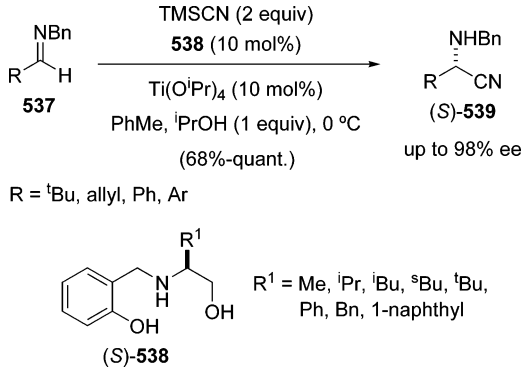
The advantages of the Strecker-type reactions have attracted many chemists to focus on the design of suitable asymmetric versions of this efficient α-AA synthesis. One of the most remarkable features of this synthesis is the easy accessibility to very important enantiomerically enriched arylglycines, which are very difficult to obtain by other preparative methods. Although enantioselective processes were unknown till the middle of the 1990s, a popular enantioselective concept is based on the use of performed imines and subsequent addition of HCN or TMSCN in the presence of a chiral catalyst. Besides asymmetric cyanations catalyzed by chiral metal complexes, several methods inspired by the use of organocatalysts have been developed during the last 2 years.[160a,436,437]

5.1.1. Strecker-Type Reactions Using Chiral Metal Complexes

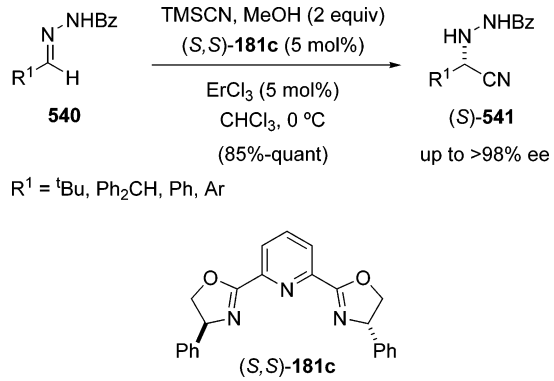
The ability of chiral metal complexes to act as versatile catalysts for a broad variety of synthetic transformations is also known for this type of transformations. The first reported enantioselective approach by Jacobsen's group[438] triggered a continuous evolution of the catalyst design for achieving the perfect asymmetric transformation involving chiral aluminum(III) **531a**, **532**, titanium(IV) **533**, **534**, scandium(III) **535**, and zirconium(IV) **536** complexes (Figure 37).[160a,436,437]

Aromatic and aliphatic aldimines were successfully tested using TMSCN as cyanide source in the presence of complexes **531a**−**536** using loadings of 5−10 mol %. The resulting α-amino nitrile derivatives were obtained, in general, in very good yields and up to 96, 95, 50, >99, 95, and 94% ee, respectively. Ketimines derived from acetophe-

Scheme 102



Scheme 103



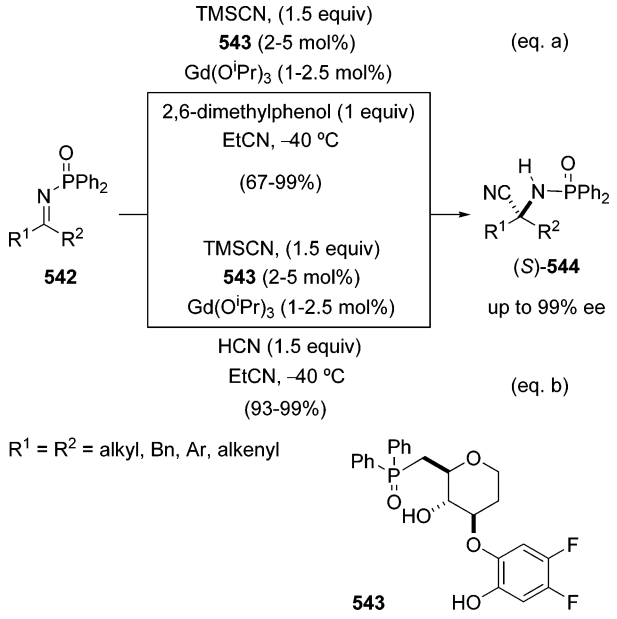
none reacted with TMSCN exclusively when aluminum and scandium complexes (R_a)-**531a** and **535** were used as catalysts, obtaining in both cases enantioselectivities up to 94%.[160a,436]

During the period of time 2004−2005, the use of this metallic catalysis decreased notably. The most suitable optically active ligands so far are salen- or binaphthol-type molecules. In general, aromatic imines are always very appropriate substrates; however, aliphatic imines and ketimines also underwent enantioselective addition under more restricted reaction conditions and catalysts (for example, employing chiral Gd complexes). The chiral metal catalysts are used in 5−15 mol %, although in some experiments catalyst charges of 1 mol %, or even less, led to excellent results.

Trimethylsilyl cyanide (TMSCN) was added to the starting imine **537** in the presence of a ligand **538**−titanium(IV) complex (10 mol %). The conversions were excellent, and the enantioselection depended on the structure and substituents of both components. The best result was achieved employing the ligand (*S*)-**538**, bearing a R^1 = 1-naphthyl as a substituent onto homoallylic imines (R = alkyl), obtaining the corresponding product (*S*)-**539** with ee > 98% after recrystallization (Scheme 102).[439] The presence of a protic additive (for example ^{i}PrOH) is essential to ensure good conversion, increasing the reaction rate and facilitating the *in situ* generation of hydrogen cyanide.

A new hydrocyanation of hydrazones **540**, catalyzed by the PyBox **181c**−lanthanide complex was optimized. Such as occurred in the preceding example, together with the TMSCN, the presence of a stoichiometric amount of methanol was also necessary, with the same function. The hydrazinonitriles (*S*)-**541** were obtained in excellent chemical yield and with very interesting ee's (up to >98%ee), especially when R^1 = Aryl (Scheme 103) and when employing erbium as the central metal atom after a systematic

Scheme 104



screening of $LnCl_3$ carried out onto molecule **540** (R^1 = Ph) under analogous reaction conditions.[440]

A significant improvement in enantioselectivity and catalyst activity was achieved for the catalytic enantioselective Strecker-type reaction of *N*-phosphinoyl ketoimines **542** mediated by a gadolinium complex with the D-glucose derived ligand **543**.[441] In a first attempt, the enantioselective Strecker-type reaction was performed in the presence of protic additives, with 2,6-dimethylphenol (DMP) being the most efficient in terms of enantioselection (up to 99% ee) and in the reduction of the reaction times (Scheme 104, eq a).[442] Nevertheless, the reaction was even faster and the required amount of the catalyst was reduced (0.1−1 mol % of gadolinium alkoxide and 0.2−2 mol % of ligand **543**) when a new modification, consisting in the substitution of DMP by hydrogen cyanide (1.5 equiv) operating at −40 °C, was introduced (Scheme 104, eq b).[443] In both reactions, the chemical yields, ee's, and purity of the crude products were very high despite the two sterically hindered substituents R^1 and R^2 of the corresponding *N*-phosphinoyl ketoimine **542**.

An approach to the enantioselective cyanation of imines has been examined employing Et_2AlCN and chiral ligands, but unfortunately, very good results were achieved using stoichiometric amounts of both the metal species and the chiral ligand.[444]

5.1.2. Strecker-Type Reactions Using Chiral Organocatalysts

The organocatalytic enantioselective Strecker-type reactions became the most successful and prolific method to obtain α-AA derivatives, to the detriment of the chiral metal complex-catalyzed ones. In this current "gold rush" state of the organocatalyst, many interesting findings are being continuously revealed. After the preliminary report of the first organocatalyzed Strecker reaction of aldimines by the *N*,*N*′-dioxide **545** (Figure 38), which was employed in stoichiometric amounts, furnishing very good enantioselections (up to 95% ee) and moderate to good yields, a large amount of functionalized organic structures have been investigated.[445] For example, ureas and thioureas catalyze stereoselectively reactions where a hydrogen-bonding inter-

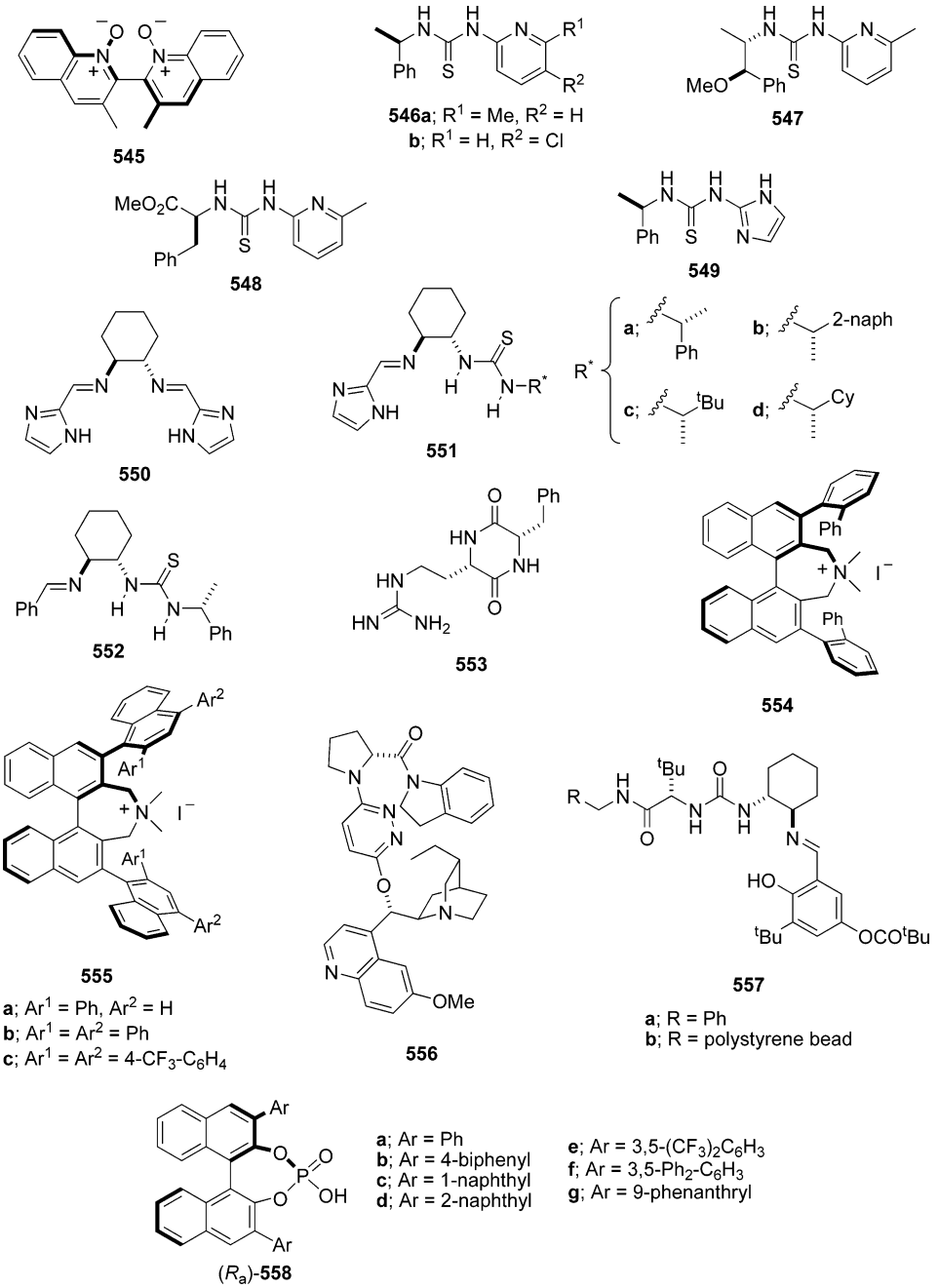
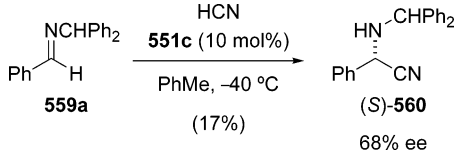


Figure 38. Chiral organocatalysts **545**−**558** employed in the enantioselective Strecker-type reactions.

action plays a crucial role in the molecular enantiodiscrimination.[446a] In recent publications, thiourea-based molecules **545**−**547** (Figure 38) were employed as bifunctional organocatalysts in the asymmetric Strecker-type synthesis onto alkyl imines, obtaining, in general, very low conversions and very poor enantioselections (up to 14% ee).[446b]

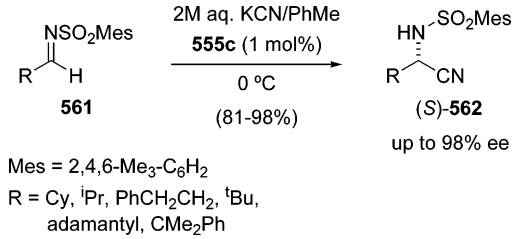
The novel chiral ligands **550**−**552** gave higher enantioselectivity when the reaction was run at −40 °C, to the detriment of the chemical yields. The cyanide source employed was hydrogen cyanide in toluene, using a catalyst charge of 10 mol %. Employing *N*-benzhydryl imines **559a** as substrates, the highest enantioselection was finally obtained with thiourea **551c** (Scheme 105), although these catalysts were more appropriate in the Michael-type addition reactions onto (*E*)-nitrostyrene.[447] The same imine also yielded a racemic mixture of product **560** in the reaction catalyzed by diketopiperazine **553** (2 mol %) using HCN in methanol at −25 °C.[448]

Scheme 105

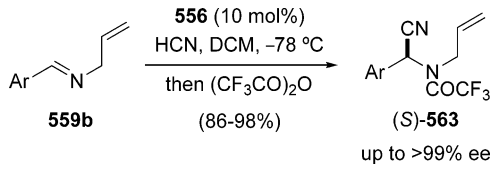


The highly enantioselective cyanation of aldimines **561** using KCN as cyanide source has been accomplished by the development of new chiral quaternary ammonium iodides **555**.[449] The evaluation of the large substituents in the binaphthyl moiety was also made using the *N*-tosylimine of cyclohexanecarboxaldehyde as a model substrate, concluding that the most suitable catalyst was **555c**. The ee's of compounds **562** were excellent (up to 98% ee) in all of the examples tested with imines derived from aliphatic aldehydes, while these conditions were not effective for aromatic

Scheme 106



Scheme 107



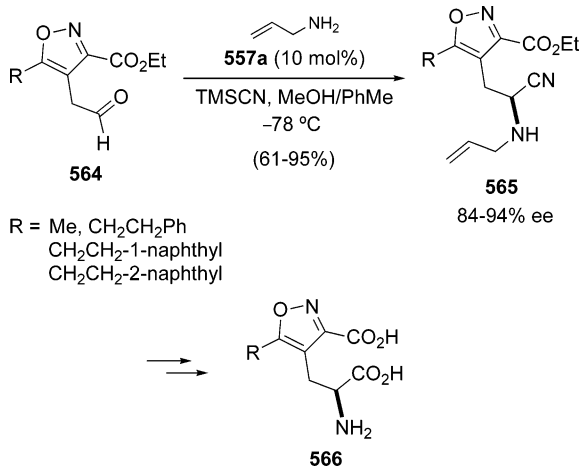
aldimines. The *ortho*-phenyl groups of the chiral ligand **555c** caused rotational restriction around the naphthyl−phenyl biaryl axes, which would provide a configurational bias to create a stereochemically defined molecular cavity over the nitrogen atom. The biphasic cyanation conditions, aqueous KCN/toluene, were uniquely successfully implemented using this type of *N*-mesitylenesulfonyl imines **561** (Scheme 106).[449]

The chiral base **556**, formed by a dihydroquinidine fragment and a segment derived from L-proline, also gave excellent results in the enantioselective Strecker-type reaction of *N*-allylbenzaldimines **559**, as also occurred in a previously reported enantioselective dihydroxylation of olefins.[450] The elevated enantioselection observed in products **563** (up to >99% ee) is in accordance with the idea that the U-shaped binding pocket in the protonated compound **556** could be used to hold the aldehyde-derived part of the aldimine, which was activated by hydrogen bonding to the protonated quinuclidine moiety present in **556** (Scheme 107). The disadvantage of the very low temperature required is counteracted by the easy and efficient recovery and further reuse of the chiral base.[450]

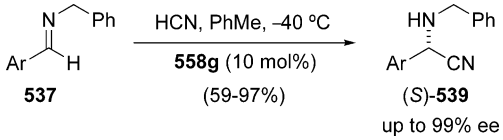
Structure−activity relationship studies of (*S*)-2-amino-3-(3-hydroxy-5-methyl-4-isoxazolyl)propionic acid (AMPA) analogues show a distinct enantioselectivity of action. Lipophilic C-5 aryl and alkyl analogues of AMPA, bearing the (*S*)-amino acid configuration, are agonists at AMPA receptors, whereas their enantiomers are antagonists or are inactive. In the enantioselective synthesis of a potent AMPA agonist, a Strecker-type reaction was performed employing the Jacobsen's ligand (*R*,*R*)-peptide **557a** and TMSCN as cyanide source. This organocatalyst allowed the one-pot, three-components sequence; that means, aldehyde, amine, and cyanide sources were put together at −78 °C. The *in situ* Schiff base formation from aldehyde **564**, circumventing the instability of the aliphatic imines, generated very high conversions of the enantiomerically enriched products **565** (84−94%), which were immediately transformed into the corresponding α-AA derivatives or into the free α-AA family **566** (Scheme 108).[451]

An organocatalytic hydrocyanation of *N*-benzoyl imines **537**, derived from aromatic or heteroaromatic aldehydes, has been reported employing hydrogen cyanide in a nonpolar solvent such as toluene at −40 °C and Binol-derived phosphates **558** as efficient Brønsted acid catalysts (Scheme 109).[452] Several examinations concerning the aryl substituents in the catalyst concluded that the best selectivities were

Scheme 108



Scheme 109

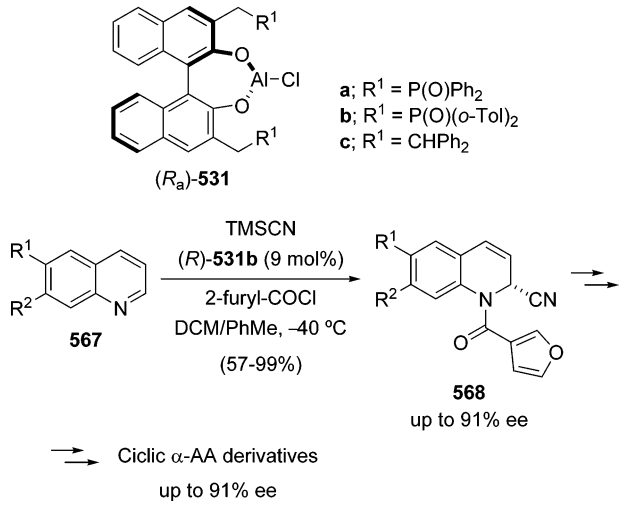


obtained with chiral phosphoric acid **558g** (Ar = 9-phenanthryl). The final products **539** were isolated with high enantioselection (up to 99% ee), due, probably, to a transition state derived from the X-ray crystal structure of the (*R*)-Binol-phosphoric acid where the imine is activated by the Brønsted acid, thereby forming an iminium species whose the *Si*-face is efficiently shielded by the voluminous phenanthryl.[452]

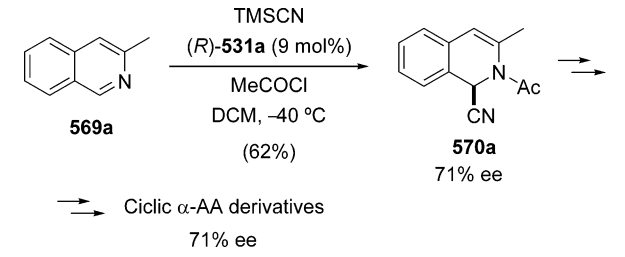
5.2. Reissert-Type Reactions

The Reissert reaction is a further transformation related to the previous described Strecker-type reaction. This reaction was discovered in 1905 by Reissert and consisted in the addition of the cyanide anion onto quinoline in the presence of benzoyl chloride. The result is a cyclic α-amino nitrile, which can be easily transformed into the corresponding cyclic α-AA.[160a,436c] The first catalytic enantioselective Reissert-type reaction was reported by Shibasaki's group employing the monometallic bifunctional catalysts[437] (R_a)-**531** onto quinolines **567** and isoquinolines **569** using TMSCN as cyanide source and 2-furoyl chloride or acetyl chloride, respectively (Schemes 110 and 111).[453] The mixture toluene/DCM turned out to represent the preferred solvent when running the reaction at −40 °C. The enantioselectivity was, in general, very high, as is shown in Scheme 110, and in order to explain it, a dual mechanism was proposed. The TMSCN would be activated by the Lewis base (oxygen atom bonded to the phosphorus) while the *N*-acylquinolinium or *N*-acylisoquinolinium species would be activated by the Lewis acid (aluminum atom).[453] This methodology allowed the enantioselective construction of a quaternary stereocenter when working with 2-substituted quinolines derived from **567** or 1-substituted isoquinolines derived from **569**, which was a valuable tool for the efficient synthesis of many useful compounds, such as, for example, the molecules MK801[454] and (−)-L689,560,[455] with the last one being a very potent noncompetitive antagonist of a subclass of receptors for the excitatory amino acid L-glutamate in brain tissue. In the key step of the synthesis of the molecule MK801, the 1-aryl

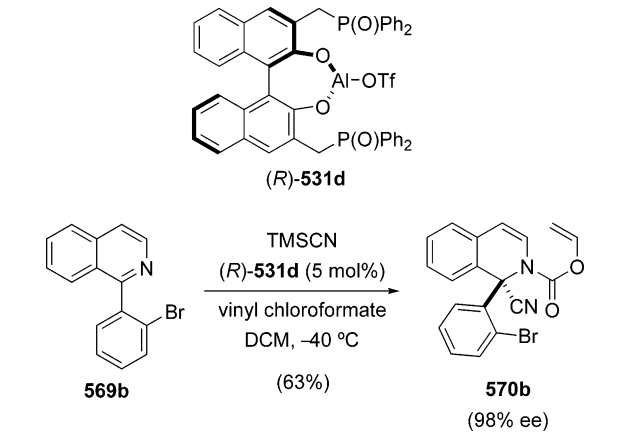
Scheme 110



Scheme 111

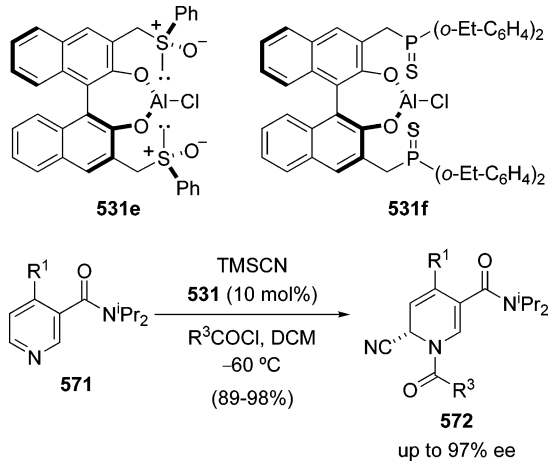


Scheme 112



substituted isoquinoline **569b** was treated with TMSCN and vinyl chloroformate as activating agent in the presence of the aluminum complex (*R*)-**531d**, obtaining the enantiomerically enriched compound **570b** with 90% ee and 63% yield (Scheme 112).[454] This result is part of a general study of the Reissert-type reaction onto 1-substituted isoquinolines when solvents, acyl chlorides, and structurally modified aluminum complexes **531** were evaluated, obtaining excellent enantioselections (up to 98% ee) when the aluminum triflate complex **531d** was employed as bifunctional catalyst.[454] However, 2-furoyl chloride and the complex **531b** were employed for the first stage of the enantioselective synthesis of agent (−)-L-689,560. The optimal reaction conditions are shown in Scheme 110, obtaining the compound **568** ($R^1 = R^2 = H$) with a 88% ee and in 91% yield.[455] In all of these examples, the cyclic α-AA derivative (ester or amide) was obtained under mild reaction conditions and maintaining the original optical purity.

Scheme 113

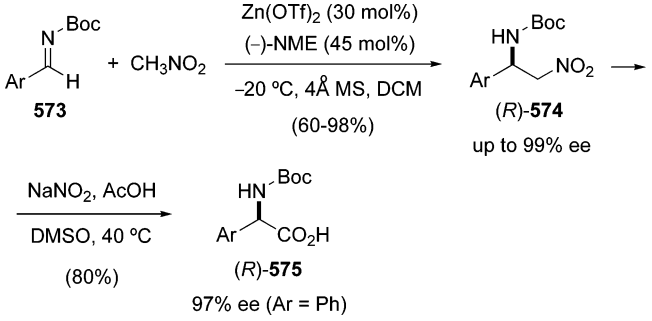


Due to the importance of chiral piperidines, the catalytic enantioselective Reissert-type reaction was also successfully essayed with TMSCN in pyridines **571** by the intermediacy of the chiral bis-sulfoxide−aluminum complex **531e** at −60 °C. In this reaction, the amido group of the starting pyridine was determined to be crucial for the obtainment of elevated enantioselectivities. Unlike the previous examples discussed, on this occasion, the nitrile group was transformed into the corresponding amine (Scheme 113). The synthetic utility of these reactions was once more demonstrated by the immediate application of this strategy to a formal catalytic enantioselective synthesis of the dopamine D_4 receptor-selective antagonist CP-293,019.[456] Also useful was the chiral aluminum complex **531** for the same reaction using more electron-deficient aromatic starting materials **571** (R^1 = Hal) in the presence of neopentyl chloroformate. Under these particular reaction conditions, compound **572** (R^1 = Hal) could be obtained in excellent yields and very high enantioselections (up to 91% ee).[456]

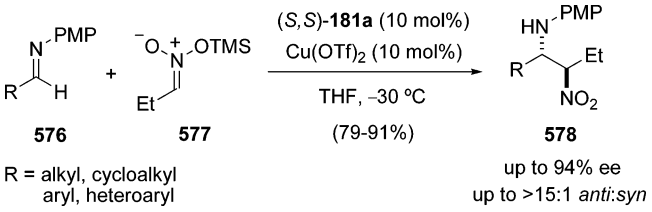
5.3. Nitro-Mannich Reactions

Nitromethane can function as a cyanide-related donor, which can be regarded as a "carboxylic acid equivalent". The conversion of the "CH_2NO_2" unit into a carboxylic acid is well-known, and it has been employed for multiple purposes.[457] The enantioselective additions of nitromethane derivatives onto imines, also called nitro-Mannich or aza-Henry reactions,[160a,436c,437a,458,459] were first reported by Shibasaki's group in 1999 using *N*-phosphinoyl imines **156** using the heterobimetallic complex [YbK_3(bi-naphthoxide)$_3$] (YbPB).[459] Binol aluminum−lithium complexes, as well as chiral bisoxazoline−[Cu] complexes, have been successfully employed in analogous transformations performed at very low temperatures.[160a] Chiral organocatalysts, such as, for example, chiral ammonium salts acting as PTC agents and thioureas, have been utilized in these transformations employing milder reaction conditions (−20 °C to room temperature).[160a] The power of the organocatalysis also involved the nitro-Mannich reaction. In fact, a few examples dealing with chiral metal complexes have been published. The complex formed by (−)-*N*-methylephedrine (NME) and Zn(OTf)$_2$ was introduced in the nitro-Mannich reaction of the *N*-Boc acyl imines **573** and nitromethane. The *β*-amino nitrocompounds **574** were obtained in very good chemical yield and elevated enantioselection (up to 99% ee). The drawback of this sequence was the high amounts of both zinc salt and

Scheme 114



Scheme 115



the chiral ligand. In this article, the synthesis of the enantiomerically enriched α-arylglycines **575** could be accomplished by treatment of (*R*)-**574** with sodium nitrite in a mixture of acetic acid and DMSO at 40 °C without racemization (Scheme 114).[460]

The complex generated by (*S*,*S*)-^{t}Bu-Box ligand **181a** (Figure 20) and $Cu(OTf)_2$ was very efficient in the reaction of *N*-(*p*-methoxyphenyl)aldimines **576** and *O*-trimethylsilyl nitropropanoate **577**. The reaction proceeded smoothly at −30 °C using anhydrous THF as solvent. Products **578** were obtained with good to very high enantioselectivities (up to 94% ee) for the major *anti*-stereoisomer (*anti*/*syn* ratio, up to >15/1) (Scheme 115).[461] This reaction did not work chemically for the *N*-(PMP)-ketimines despite modification of some reaction parameters.

By contrast, the number of chiral organocatalysts tested (Figure 39) is more abundant, and several articles reflect the high activity of such molecules in the asymmetric nitro-Mannich reaction. Ricci's[462] and Palomo's[463] groups independently reported practically the same work at the same time, consisting in the aza-Henry reaction between *N*-Boc imines **573a** or α-amido sulfones **584** and nitromethane catalyzed by the chiral ammonium salt derived from quinine **234y** (10 mol %). The advantages of using the α-amido sulfones **584** are evident, because the synthesis of some *N*-Boc-imines is somewhat difficult to achieve, and with this strategy, the amine has to be Boc-protected and the imine is generated *in situ*. In both cases, the authors realized that *N*-Boc imine **573a** did not react as well, in terms of enantioselection, as the α-amido sulfones **584**, obtaining compounds **574a** with moderate ee's (Scheme 116). Ricci and co-workers found the same results using KOH as base and running the reaction at −45 °C, and they also concluded that α-amido *p*-tolyl sulfones, rather than phenyl sulfones, afforded compounds **574** with higher enantioselectivities.[463] In addition, when the reaction was carried out with α-aryl-α-amido sulfones **557** in the presence of nitroethane, also high enantioselection (up to 98% ee) of the major *syn*-diastereoisomer was detected (up to 95:5 *syn*/*anti* ratio)[462] and no further transformation was directed to the synthesis of α-AA derivatives (Scheme 116, eq a). The second contribution performed a screening of chiral PTC agents **234a**, **234y**, **579**, and **580** together with inorganic bases for the reaction of **573a** and nitromethane, obtaining the best result when the couple **234y** (12 mol %)/$CsOH{\cdot}H_2O$ was employed (Scheme 116, eq b).[463]

Bifunctional thiourea **581b** catalyzed the aza-Henry reaction of nitroalkanes with *N*-Boc-imines rather than the other *N*-protected imines to give *syn*-*β*-nitroamines **574** with good to high diastereo- (up to 94% de) and enantioselectivity (up to 99% ee) (Scheme 117). However, the *N*-phosphinoyl imines **156** gave the opposite absolute configuration. Several other thioureas **581a** and **582b** also promoted this reaction but with lower enantioselectivity. On this occasion, the products **574** were not transformed into α-AA derivatives

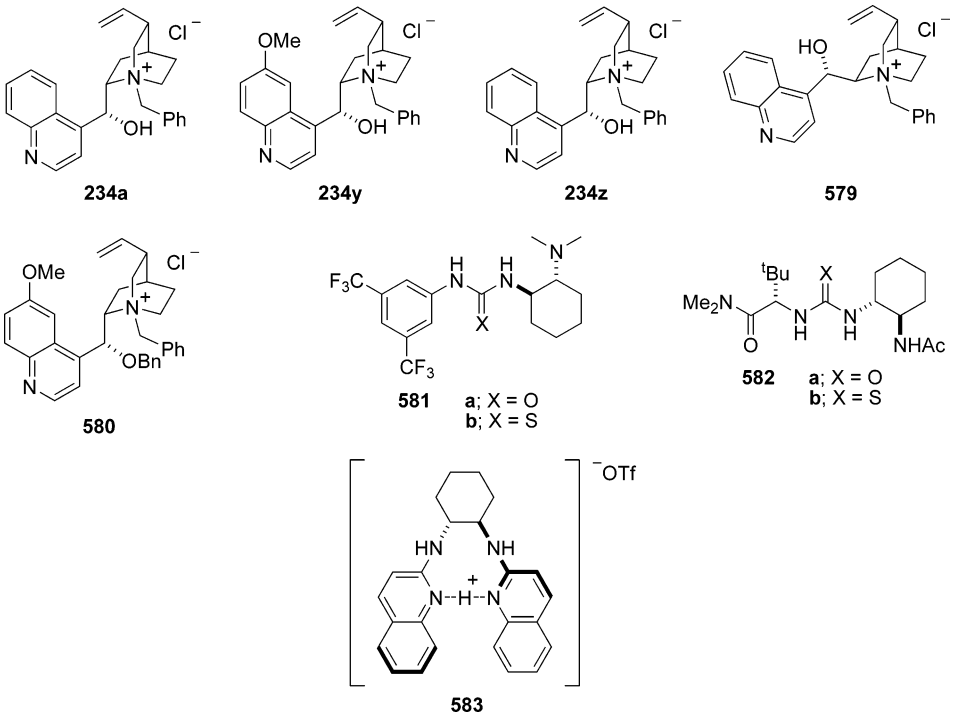
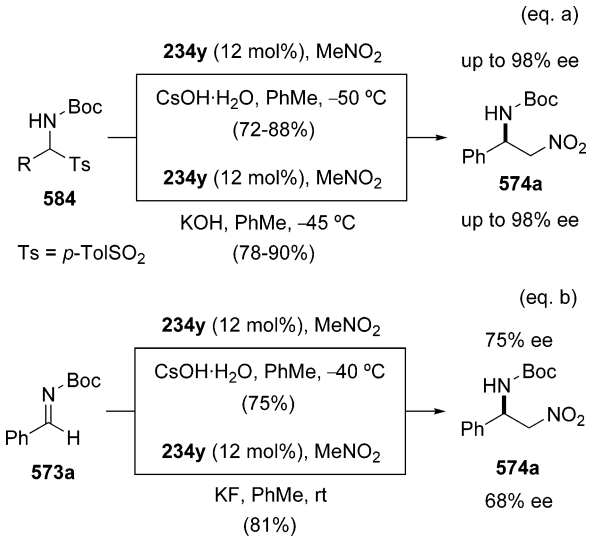
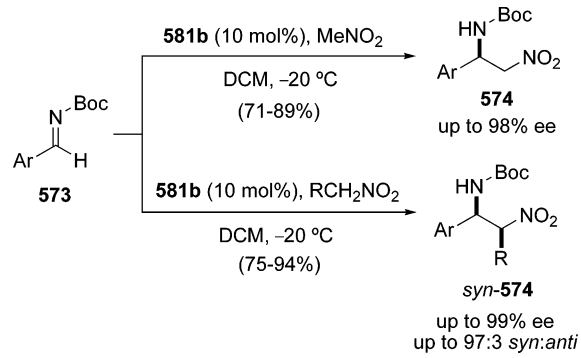


Figure 39. Recent organocatalysts tested in the nitro-Mannich reactions onto *N*-substituted imines.

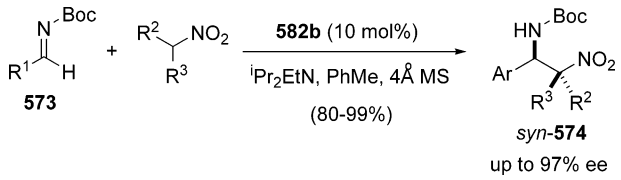
Scheme 116



Scheme 117



Scheme 118

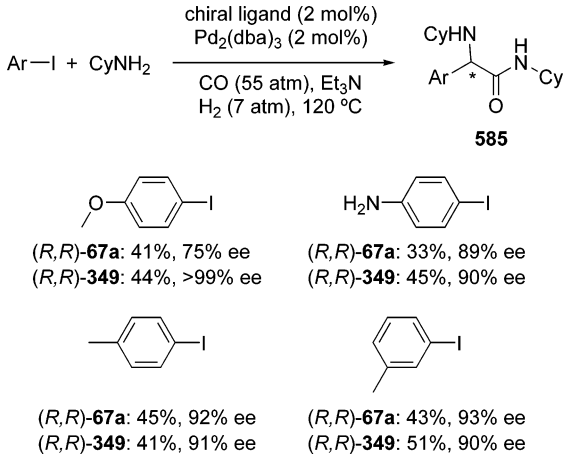


but into other interesting intermediates, which gave access to biologically important piperidines such as, for example, CP-99,994, which may be of potential therapeutic value. The dual role of the thiourea groups seems to be clear: the activation of the *N*-Boc-imine by the two hydrogen bonding interactions and the activation of the nitroalkene by the *N*,*N*-dimethylamino terminus can be postulated between different mechanistic scenarios.[464]

Ureas and thioureas **582** and its derivatives, and **583** (Figure 39) were tested in the nitro-Mannich reaction of *N*-Boc-imines **573** with nitroethane, 1-nitropropane, 2-nitropropane, and *β*-functionalized nitroethanes, obtaining excellent enantioselections and very high *syn*/*anti* diastereomeric ratios. The most appropriate organocatalyst was the thiourea **582b** (10 mol %) together with 4 Å molecular sieves and the Hünig's base in toluene at 4 °C (Scheme 118). A dual activation of both nucleophile and electrophile was firmly postulated on the basis of preceding experimental findings.[465]

The already mentioned hydrogen bonding interactions, such as those responsible for these enantioselections, were supported by the catalysis of the nitro-Mannich reaction between *N*-Boc-arylimines and nitroalkanes by a chiral

Scheme 119



proton source (or polar ionic hydrogen bond) such as, for example, the bisamidine ligand **583**. In general, the yields were good to moderate (50−69%) and the enantioselectivity was noticeable (59−95% ee), with a very good *syn*-diastereoselectivity (up to 19/1 *syn*/*anti* ratio) being achieved. The employment of this Brønsted acid represents a significantly lower cost and toxicity compared to the traditional Lewis acid complexes, and also salt **583** can be removed from the final reaction by extractive workup.[466]

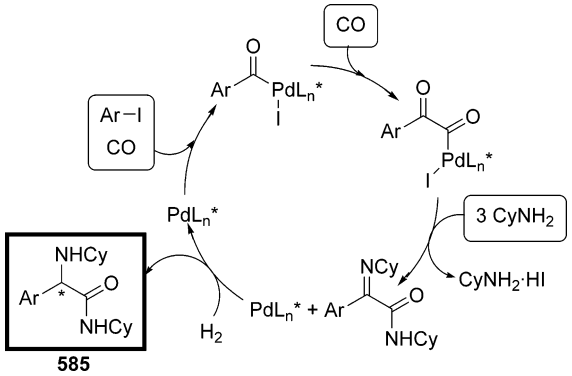
6. Enantioselective Multicomponent Assembly

In the preceding sections, the enantioselective procedures have been classified according to the segment of the α-AA introduced. Traditionally, Strecker and Ugi's multicomponent synthesis of α-AA is based on this strategy, but unfortunately, (see previous section) there is not any enantioselective surrogate of these two known methods.[467] In this way, the amino group, the hydrogen at the α-position, and the carboxylic group can be introduced (Scheme 1, eq o), following the pioneering work of Alper's group describing a palladium catalyzed double carbohydroamination, amine condensation, and hydrogenation.[313c,468] This novel domino reaction created for the one-pot production of α-AA derivatives is very simple in execution and workup, and it possesses considerable synthetic potential.[469]

The asymmetric synthesis of the titled compounds using this sequence has been reported by the same group. The $[Pd_2(dba)_3]$ was the palladium source employed, together with chiral ligands (*R*)- or (*S*)-Binap **87a** (Figure 13), (*R*,*R*)-Me-DuPhos **67a** (Figure 11), (*S*)-*p*-Tol-Binap **144** (Figure 17), and Trost's ligand (*R*,*R*)-**349** (Figure 30). The experiments were conducted by using an aryl iodide, cyclohexylamine, carbon monoxide (55 atm), hydrogen (7 atm), the catalyst, and 4 Å MS in methanol or triethylamine at 120 °C, and outstanding results were attained (up to >99% ee) using (*R*,*R*)-Me-DuPhos **67a** and Trost's ligand (*R*,*R*)-**349** but with moderate chemical yields of **585** due to the complexity of these domino reactions under these hard conditions (Scheme 119).[470] The amides **585** were not transformed into the corresponding α-AAs despite an additional hydrolysis protocol that would lead directly to them. Perhaps, the racemization of the stereogenic center is the major drawback of this transformation, which would be overcome by the introduction of a different nitrogen substituent.

A possible pathway for the formation of α-amido amines **585** derived from aryl glycines, whose absolute configura-

Scheme 120



tions were not supplied, may involve, according to the side products obtained in different reaction stages, a double carbonylation, followed by amine condensation and final hydrogenation (Scheme 120). It is logical to assume that the last step, the final introduction of the hydrogen at the α-position, is the enantioselective step in the synthesis of **585**.[470]

7. Conclusions

As we can deduced from the contents of this review, a plethora of chiral catalytic systems have been developed for the highly enantioselective synthesis of the α-AA framework; however, new studies and different metal catalysts and organocatalysts are continuously emerging in the search for the perfect catalytic system. This exciting area of organic synthesis, which generates one of the most important compounds in the cycle of terrestrial life, incorporates and adapts whatever type of reaction, methodology, or enantiodiscrimination processes have already been published with other different purposes. Classical hydrogenations of DAA derivatives and electrophilic alkylations of glycine derivatives under chiral PTC reactions are the most powerful and studied areas. Nevertheless, this does not mean that other strategies are less important. Rather, they are complementary to each other in order to facilitate the synthesis of the desired α-AA. The employment of *Cinchona* derived PTC agents is nowadays the most reliable method to obtain a large range of α-AAs in very high yields and excellent enantioselections using very small amounts of catalyst and mild operating conditions. The recovery of the employed catalyst is another attractive scientific aspect that should always be considered because it would allow the synthesis in larger scale production.

8. Acknowledgments

We are grateful to Dr. M. J. Muñoz for her valuable help. We thank the Spanish Ministerio de Educación y Cultura (MEC) for continuous support and Generalitat Valenciana (CTIOIB/2002/320, GRUPOS03/134, and GV05/144) and the University of Alicante for financial support.

9. Note Added in Proof

During the editorial galley proof corrections, a new review, dealing with the asymmetric synthesis of α,α-disubstituted α-amino acids, was published: Vogt, H.; Bräse, S. *Org. Biomol. Chem.* **2007**, *5*, 406.

10. References

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CR050580O