Recent Advances on Asymmetric Nitroso Aldol Reaction

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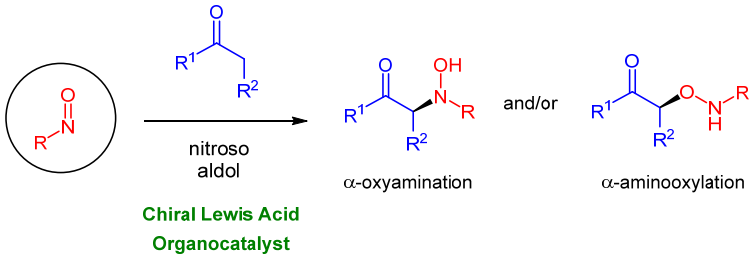
Graphical Abstract



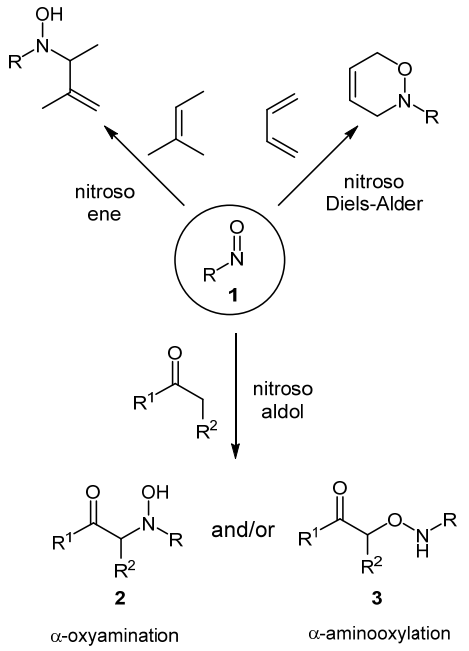
Biographical Sketch

Abstract

The reaction of aromatic nitroso derivatives with enolizable carbonyl compounds (nitroso aldol reaction) to give either α-hydroxyamino or α-aminoxycarbonyls is an important synthetic method. This review illustrates the recent advances in rendering the process regio- and enantioselective as well as catalytic. By employing metal and organic catalysts one can generate a range of α-amino (α-oxyamination) and α-hydroxy (α-aminoxylation) carbonyl derivatives with total regioselectivity and high levels of enantiomeric excess.

1. Introduction

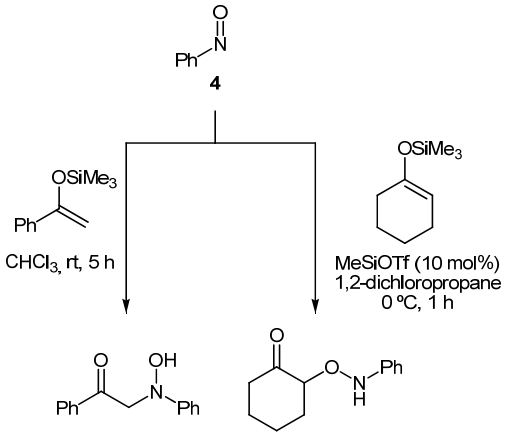
The introduction of amino and oxygen functionalities in an organic molecule is among the most important tools employed in synthetic chemistry, particularly if it is achieved in an enantioselective way. Chiral molecules bearing amino and/or hydroxy groups are ubiquitous in natural products and therapeutic drugs; also, they are of a great utility as synthetic intermediates. Of particular interest are those derivatives in which the heteroatom is in proximity to other reactive functional group, like a carbonyl, that allow for further chemical elaboration. In this context, organic nitroso compounds **1** are valuable intermediates because of the particular reactivity of the nitroso group[1,2] that allow multiple reactivity as *N*- and *O*-electrophiles in amination and hydroxylation reactions, respectively (nitroso aldol)[3] as well as enophiles in cycloaddition reactions (Scheme 1).[4] Both the nitroso ene[5-7] and nitroso Diels-Alder[8-11] reactions have been studied widely.



Scheme 1. Main reactivity of nitroso compounds

The main problem of the nitroso aldol reaction is the regioselectivity. If the addition takes place on the nitrogen atom of the nitroso group, α-amino carbonyls **2** are obtained, through an α-oxyamination process. On the other hand, when the addition take place on the oxygen atom of the nitroso group, α-hydroxy carbonyls **3** are obtained through a typical α-aminoxylation reaction. In some instances, the term "nitroso aldol reaction" only refers to the α-oxyamination process by analogy between N=O and C=O funtionalities whereas the term "α-aminoxylation" is preferred for the *O*-selective

reactions. Since both processes correspond to the reaction between a carbonyl group and a nitroso compound we will consider both of them in this revision. In general, the regioselectivity of the reaction can be controlled by the action (or absence) of a Lewis acid. Whereas the reaction proceeds through *N*-addition with *in situ* generated or preformed enolates (usually, lithium, tin or silicon),[12] *O*-addition is observed if the reaction is catalyzed by a Lewis acid (Scheme 2).[13] In addition to trimethylsilyl triflate, various metal ions including copper, cobalt, iron, silver, gold and hafnium promote an *O*-selective nitroso aldol reaction.[14] It has been suggested[15] that in the Lewis acid promoted reaction, the aminooxy compounds could come from a nitroso dimer generated *in situ* in the presence of the Lewis acid. Simple enolates would give rise to hydroxyamino compounds through the nitroso monomer.



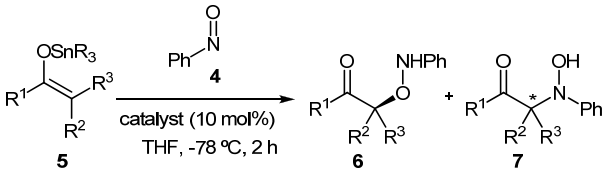
Scheme 2. Regioselective nitroso aldol reactions

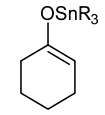
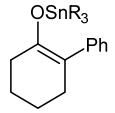
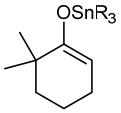
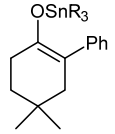
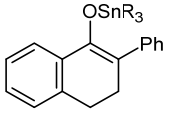
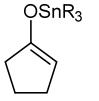
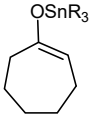
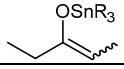
In the last years, remarkable advances have been made in the use of nitroso compounds for preparing α-amino and α-hydroxy carbonyl compounds in an enantioselective way through asymmetric α-aminoxylation[16] and α-oxyamination[17] reactions, respectively. Some aspects of nitroso aldol reaction have been included as a part of more general reviews,[1,3,4] including those dedicated to the highly reactive nitrosocarbonyl compounds.[18] This review aims to provide coverage -from the last 15 years- of recent advances in nitroso aldol reactions mainly considering both metal-catalyzed and organocatalyzed processes. In addition to nitroso aldol reactions with aldehydes and ketones, we review reactions of related enamines with nitroso compounds. The review has been categorized by the type of catalysis. For the sake of clarity, differences in regioselectivity have been discussed when necessary for each particular case.

2. Metal-Catalyzed Reactions

A general asymmetric *O*-selective nitroso aldol reaction was developed using tin enolates derived from ketones and nitrobenzene. Optimization studies led to the identification of catalysts that produce excellent regio- and enantioselectivities for a range of alkyl and aryl-substituted tin enolates. The catalysts consisted of BINAP-silver complexes formed by combining (*R*)-BINAP and (*R*)-TolBINAP with silver salts such as AgOTf and $AgClO_4$ (Table 1).[19] The reaction was independent of any variation in cyclic tin enolate, although tributyl tin enolates had slightly increased *N*-selectivity. Taking into account that *N*-selective nitroso aldol reactions occur in the absence of catalyst, a competitive experiment between tributyl and trimethyl tin enolates demonstrated that the higher reactivity of tributyltin enolates resulted in more significant uncatalyzed process.

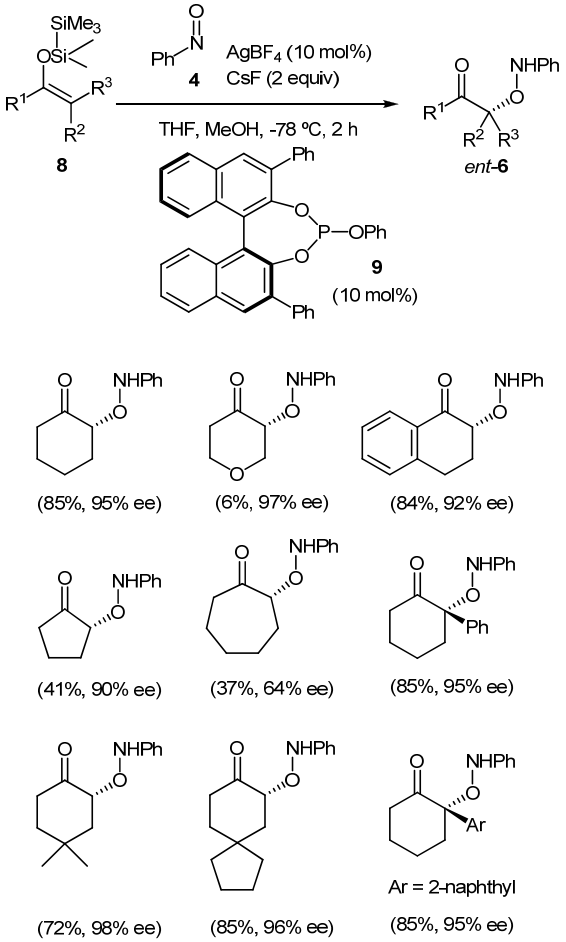
Table 1 *O*-Nitroso Aldol Reaction of Tin Enolates[a]



enolate	R	catalyst[b]	yield (%)	6:7	ee% of 6
	Bu	A	95	>99:1	95
	Bu	B	92	>99:1	91
	Bu	C	93	>99:1	92
	Me	B	95	>99:1	97
	Me	C	94	>99:1	94
	Me	B	78	>99:1	96
	Bu	A	97	85:15	91
	Bu	C	97	83:17	95
	Bu	B	96	>99:1	95
	Me	C	97	>99:1	88
	Me	B	94	>99:1	87
	Bu	C	90	66:34	85
	Me	B	92	>99:1	90
	Me	C	96	>99:1	85
	Me	B	93	>99:1	92
	Bu	C	90	91:9	85
	Me	B	95	92:8	82
	Me	B	92	81:19	94

a Reactions were conducted with 1.0 equiv of nitrosobenzene and 1.0 equiv of tin enolate. [b] Catalyst A: (R)-BINAP·$AgClO_4$. Catalyst B: (R)-TolBINAP·AgOTf. Catalyst C: (R)-TolBINAP·$AgClO_4$.

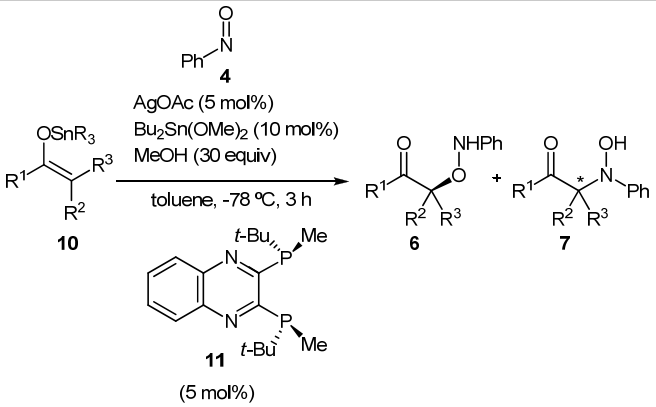
The reaction was extended, with excellent results, to less toxic disilanyl enol ethers **8** by using silver tetrafluoroborate as silver source and 3,3'-diphenyl (*S*)-binol-derived phosphite **9** as a ligand (Scheme 3).[20] The reaction required an excess of cesium fluoride to proceed.

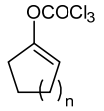
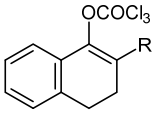
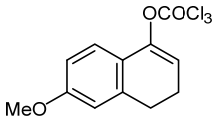
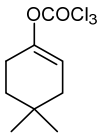
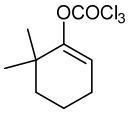
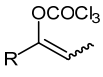


Scheme 3

α-Aminooxy ketones were prepared with enantioselectivities of up to 99% from alkenyl trichloroacetates **10** by using *t*-Bu-QuinoxP* **11** in complex with AgOAc as the chiral catalyst and dibutyl(methoxy)-λ^3-stannane as the achiral cocatalyst (Table 2).[21] The reaction, which is not completely *O*-selective, seems to proceed through a tin enolate formed *in situ* which adds enantioselectively to nitrosobenzene in the presence of the chiral catalyst. The driving force of the catalytic cycle originates from the rapid methanolysis of an intermediate tin amide.

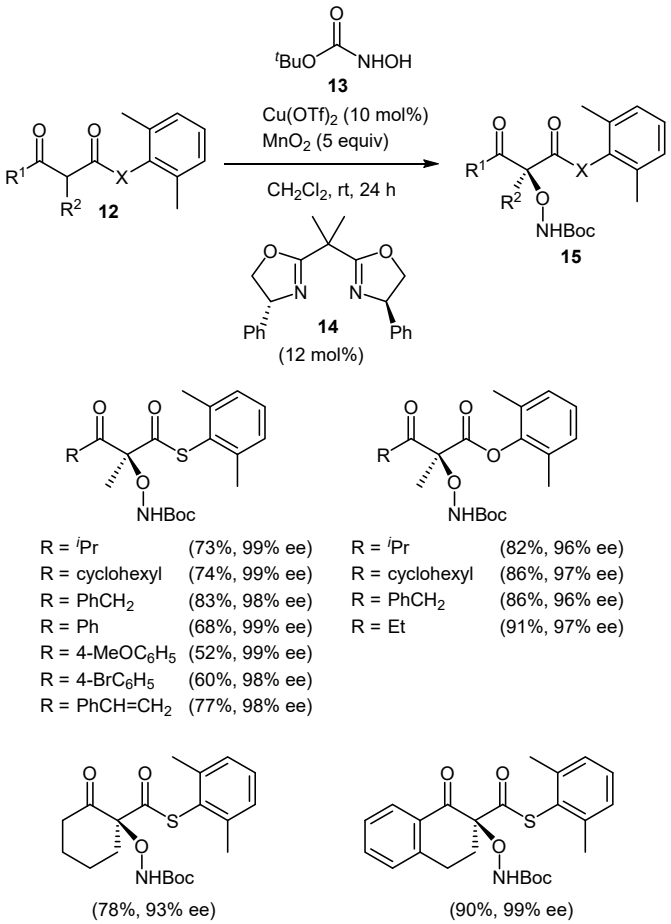
Table 2 *O*-Nitroso Aldol Reaction of alkenyl trichloroacetates[a]



enolate		yield (%)	**6**:**7**	ee% of **6**
	n = 1	81	76:24	97
	n = 2	65	89:11	99
	n = 3	72	68:32	96
	R = H	92	>99:1	99
	R = Me	24	82:18	95
		90	96:4	97
		68	91:9	97
		71	97:3	97
	R = Ph	8	51:49	92
(*E*/*Z* = 1/4)	R = Et	21	<1:99	3

a Reactions were conducted with 1.0 equiv of nitrosobenzene and 2.0 equiv of alkenyl trichloroacetate.

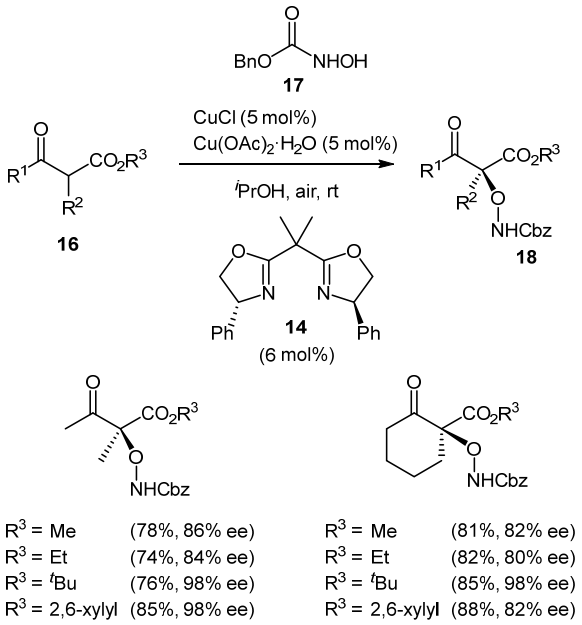
The first example of Cu-catalyzed *O*-nitroso aldol reaction has been reported by Yamamoto and co-workers.[22] The methodology was applied to β-keto(thio)esters **12** and highly enantioenriched α-aminooxy-β-ketoesters **15** were prepared (Scheme 4). The nitroso derivative was generated *in situ* from the commercially available *N*-Boc hydroxylamine **13** and manganese(IV) as an oxidant. The reaction was conducted in the presence of copper(II) triflate and bisoxazoline (*R,R*)–PhBox **14** as ligand. The slow addition of *N*–Boc–hydroxylamine was crucial to avoid condensation between the *in situ* formed nitrosocarbonyl species and excess **13**. The reaction showed a high preference for *O*-selectivity and only traces of *N*-nitroso carbonyl aldol were detected.



Scheme 4

The reaction has also been carried out by generating the nitroso derivative under aerobic oxidation conditions from the corresponding *N*-(benzyloxycarbonyl) hydroxylamine **17**. The procedure involved mixing of all reagents at room temperature and illustrated a fully catalytic process in both oxidation and enolization processes.[23] A combination of copper(I) chloride and copper(II) acetate was used as Lewis acid; chirality was induced by using ligand **14** (Scheme 5). Notably, when copper(II) acetate was replaced by copper(II) triflate and no chiral ligand was added the reaction was *N*-selective providing, obviously, racemic substrates.[24]

The choice of the ester was crucial for achieving good values of enantioselectivity, the more sterically demanding groups (e.g. *tert*-butyl and 2,6-xylyl) giving rise to the best values.



Scheme 5

A model of addition has been suggested based on the experimental observations (Figure 1). Read de Alaniz and co-workers proposed[23] the approach of the nitrosocarbonyl to the catalyst-coordinated β-ketoester by the same face in which the counterion occupies an axial position, thus preventing both coordination of the nitroso species to the Lewis acid and unfavourable steric interactions between the protecting group of the nitroso species and the complex. In agreement with this proposal is the observation that bulkier protecting groups, such as Boc, provided better enantioselectivities.[22]

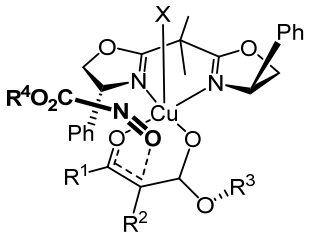
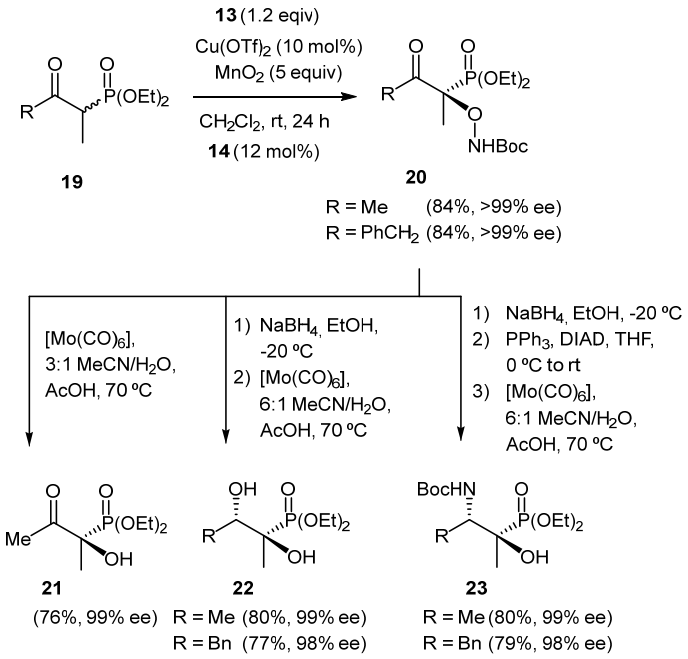


Figure 1. Model of addition for Cu-catalyzed nitroso aldol reaction (X = counterion)

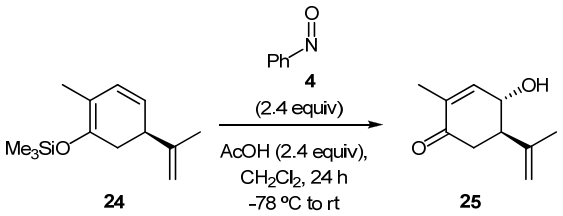
Application of the methodology illustrated in Scheme 4 allowed preparation of substituted α-aminooxyphosphonates **20** of synthetic utility when β-ketophosphonates **19** were employed as starting materials. An example is illustrated in Scheme 6 showing the possibility of obtaining α-hydroxyphosphonates **21**, α,β-dihydroxyphosphonates **22** and β-amino-α-hydroxyphosphonates **23**.[25] The reaction proceeded in very good yields and enantioselectivities with both acyclic and cyclic substrates at the ketone moiety. On

the other hand, compounds bearing an ester (Scheme 6, R = OMe) or thioester (Scheme 5, R = SPh) in place of the ketone group gave no reaction.



Scheme 6

The vinylogous nitroso Mukaiyama aldol reaction has been reported by using silyl enolates derived from α,β-unsaturated esters as starting materials and acetic acid or HF·Py as promoters.[26] Nitrosobenzene was added in an excess thus promoting the N-O cleavage of the *in situ* generated γ-aminoxy species. Under such conditions racemic γ-hydroxy α,β-unsaturated esters were obtained. When the reaction was conducted with silyl enolate **24** derived from (-)-carvone, enantiomerically pure (+)-5α-hydroxycarvone **25** was obtained (Scheme 7).

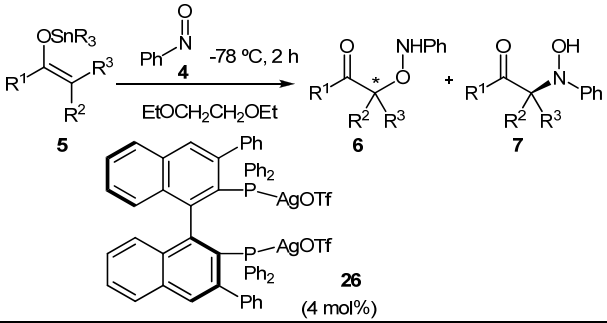


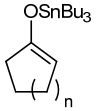
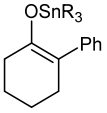
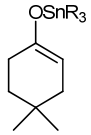
Scheme 7

The first example of a catalytic enantioselective *N*-nitroso aldol reaction was reported using BINAP-silver complexes[27] which were developed based on previously reported asymmetric catalysts that promote *O*-selective reactions.[19] In particular, for the reaction between tin enolates and nitrosobenzene, whereas AgOTf, AgOAc and $AgOCOCF_3$-derived 1:1 complexes with (*R*)-BINAP were shown to be efficient catalysts in *O*-selective nitroso aldol reactions (see above), the reaction catalyzed by the 2:1 complex

26, generated from 0.4 equiv of (*R*)-BINAP for AgOTf, resulted completely *N*-selective affording high enantioselectivites (Table 3).

Table 3 *N*-Nitroso Aldol Reaction of Tin Enolates[a]

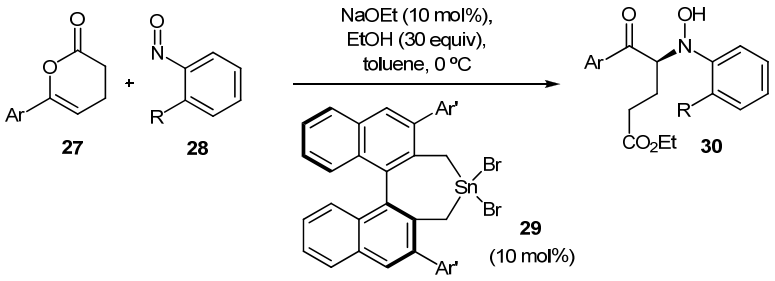


enolate	R	yield (%)	**6**:**7**	ee% of **7**
	n = 1	90	3:97	86
	n = 2	95	4:96	>99
	n = 3	96	<1:99	97
		94	<1:99	77
		97	<1:99	98

[a] Reactions were conducted with 1.0 equiv of nitrosobenzene and 1.0 equiv of tin enolate.

Alkenyl trichloroacetates have been reported to undergo *N*-nitroso aldol reactions with nitrosobenzene using dibutyltin dimethoxide as a catalyst, which is regenerated by methanol.[28] However, no chiral version of the reaction has been developed. On the other hand, the same group reported the catalytic enantioselective *N*-nitroso aldol reaction of γ,δ-unsaturated δ-lactones **27** using a chiral tin bromide ethoxide as a catalyst generated *in situ* from the corresponding tin dibromide **29**.[29] Notably, the reaction took place smoothly providing high enantioselectivities with nitrosoarenes **28** bearing a bulky substituent at *ortho*-position; on the contrary, with nitrosobenzene (**28**, R = H) both yield and enantioselectvity were low (Table 4). In general, no traces of the *O*-adduct were detected. With β,γ-unsaturated γ-lactones lower chemical yields and enantioselectivities were obtained.

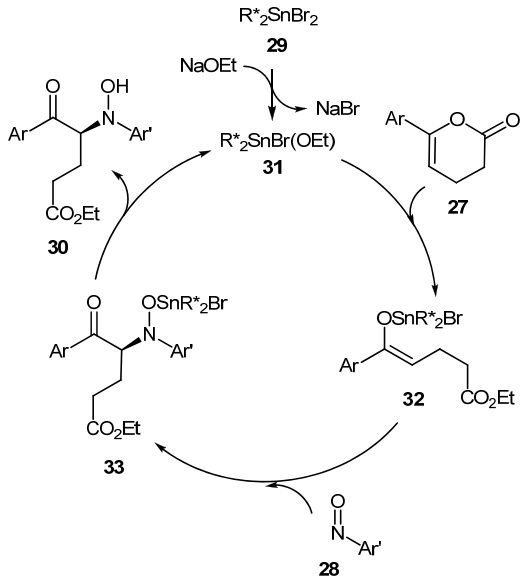
Table 4 *N*-Nitroso Aldol Reaction of γ,δ-unsaturated δ-lactones[a]



Ar	R	time (h)	yield (%)	ee %
Ph	H	12	27	49
Ph	F	12	87	57
Ph	Br	12	73	38
Ph	CF_3	12	93	43
Ph	$^{i}C_3H_7$	12	82	90
4-MeC_6H_4	$^{i}C_3H_7$	12	94	95
4-$MeOC_6H_4$	$^{i}C_3H_7$	12	97	92
2-FC_6H_4	$^{i}C_3H_7$	12	75	>99
4-BrC_6H_4	$^{i}C_3H_7$	12	92	95
2-naphthyl	$^{i}C_3H_7$	16	>99	98
Ph	$^{t}C_4H_9$	12	37	99
4-MeC_6H_4	$^{t}C_4H_9$	12	30	97
4-BrC_6H_4	$^{t}C_4H_9$	12	73	96

[a] Reactions were conducted with 1.0 equiv of nitrosoarene and 2.0 equiv of γ,δ-unsaturated δ-lactone.

The authors suggested the catalytic cycle illustrated in Scheme 8. According to this proposal the reaction of dibromide **29** with sodium ethoxide generates *in situ* the real catalyst **31** which reacts with **27** to form tin enolate **32**. Further nitro aldol reaction between **32** and **28** affords intermediate **33** which regenerates the catalyst upon releasing product **30**.

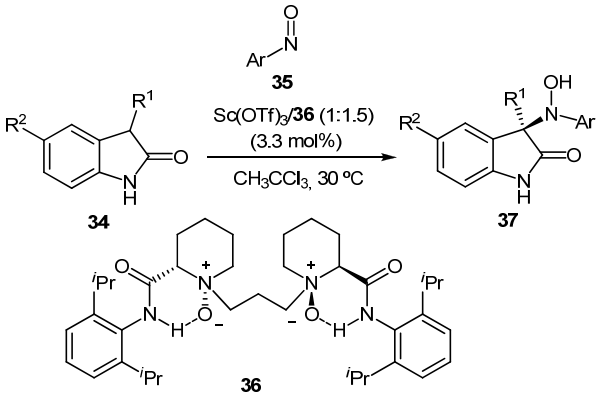


Scheme 8.

A highly efficient catalytic asymmetric hydroxyamination of *N*-unprotected-3-substituted oxindoles **34** has been reported by Feng and co-workers.[30] The reaction was

carried out with a 1:1.5 complex formed *in situ* from scandium(III) triflate and bis-N-oxide **35**. The reaction conditions were tolerant with several functional groups and provided high yields and enantioselectivities in a totally *N*-selective nitroso aldol reaction (Table 5). The reaction leading to highly enantioenriched quaternary centers was carried out with a variety of nitrosoarenes demonstrating a good versatility in both oxindoles and nitrosoderivatives.

Table 5 *N*-Nitroso Aldol Reaction of Oxindoles[a]

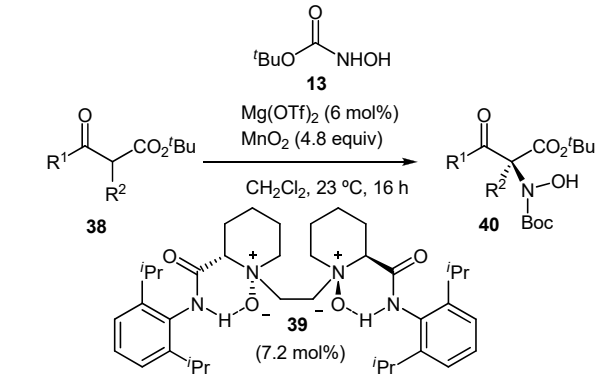


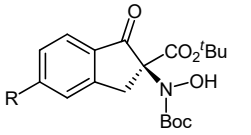
R^1	R^2	Ar	t (h)	yield (%)	ee %
Me	H	Ph	0.3	92	95
Me	H	2-ClC_6H_4	0.5	88	90
Me	H	3-ClC_6H_4	1	92	94
Me	H	4-BrC_6H_4	0.5	90	92
Me	H	2-MeC_6H_4	0.5	66	92
Me	H	3-MeC_6H_4	1	90	88
Me	H	4-MeC_6H_4	1	85	89
Me	H	4-$MeOC_6H_4$	3	95	92
Et	H	Ph	1	91	92
^{n}Pr	H	Ph	0.5	92	90
^{n}Bu	H	Ph	0.5	89	92
allyl	H	Ph	0.5	98	94
benzyl	H	Ph	1	97	95
4-$MeOC_6H_4CH_2$	H	Ph	1	94	97
piperonyl	H	Ph	1	93	94
3-$PhOC_6H_4CH_2$	H	Ph	1	95	95
4-$PhC_6H_4CH_2$	H	Ph	1	90	90
2-$ClC_6H_4CH_2$	H	Ph	0.5	92	90
4-$ClC_6H_4CH_2$	H	Ph	0.5	93	94
2,4-Cl_2-$C_6H_3CH_2$	H	Ph	0.5	91	95
4-$BrC_6H_4CH_2$	H	Ph	0.5	93	97
2-naphthylmethyl	H	Ph	1	95	98
2-(thienyl)methyl	H	Ph	1	89	92
2-(pirydyl)methyl	H	Ph	1	93	92
Me	Br	Ph	0.5	98	90
Me	Me	Ph	0.3	92	91
Me	MeO	Ph	0.3	90	91

[a] Reactions were conducted with 1.1 equiv of nitrosobenzene and 1.0 equiv of oxindole.

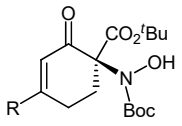
Ligand **39**, rather similar to **36**, was employed in the magnesium-catalyzed asymmetric hydroxyamination of cyclic and acyclic β-ketoesters **38** (Scheme 9).[31] In all cases complete *N*-selectivity as well as high yields and enantioselectivities were observed.

The nitrosoformate derivative was generated *in situ* from the corresponding carbamate **13** and manganese(IV) oxide.[32] In contrast to the reaction catalyzed by copper(II) triflate (see above Scheme 4), when bisoxazolines such as PhBox **14** were used as ligands considerably lower enantiomeric excesses were obtained although the *N*-adducts were predominant (15:1 *N/O* ratio). The reaction was also extended to benzyloxycarbamate **17** without substantial loss of any selectivity.

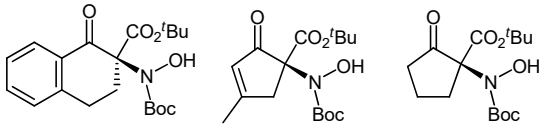




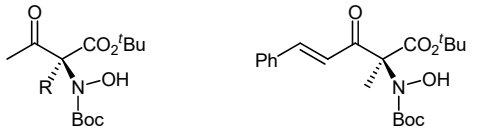
R^1 = H R^2 = H (91%, 95% ee)
R^1 = F R^2 = H (94%, 95% ee)
R^1 = H R^2 = MeO (89%, 93% ee)
R^1 = H R^2 = CF_3 (88%, 93% ee)



R = H (95%, 93% ee)
R = Me (97%, 96% ee)
R = EtO (97%, 96% ee)



(95%, 86% ee) (83%, 93% ee) (92%, 85% ee)



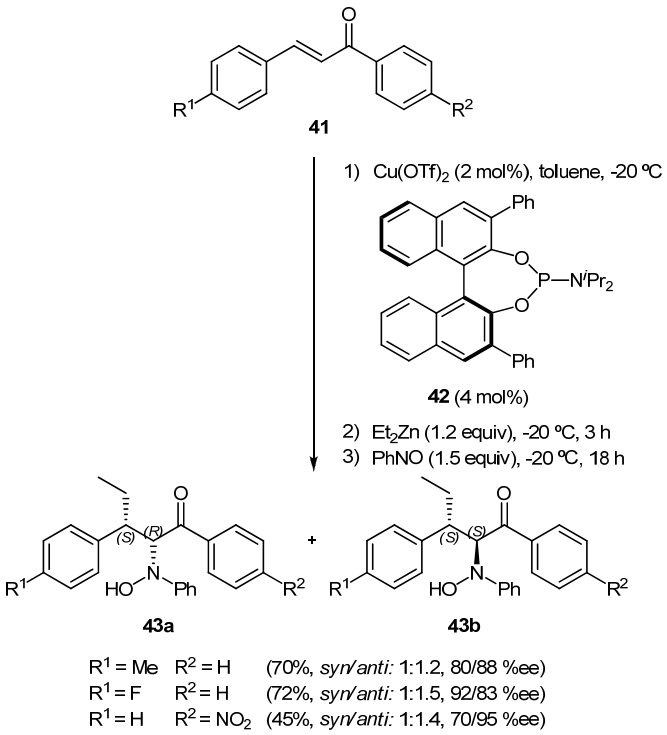
R = Me (89%, 94% ee)
R = $PhCH_2$ (95%, 93% ee)
R = allyl (88%, 94% ee)
R = propargyl (82%, 94% ee)

(89%, 87% ee)

Scheme 9.

Liu and co-workers reported an enantioselective tandem conjugate addition / *N*-nitroso aldol reaction catalyzed by copper(II) triflate and phosphoramidite **42** in the presence of equimolar amounts of diethylzinc.[33] The first step of the reaction consisted on the conjugate addition of ethyl zinc to **41**. The intermediate chiral zinc enolate formed after the addition was trapped with nitrosobenzene **4** through a typical nitroso aldol reaction

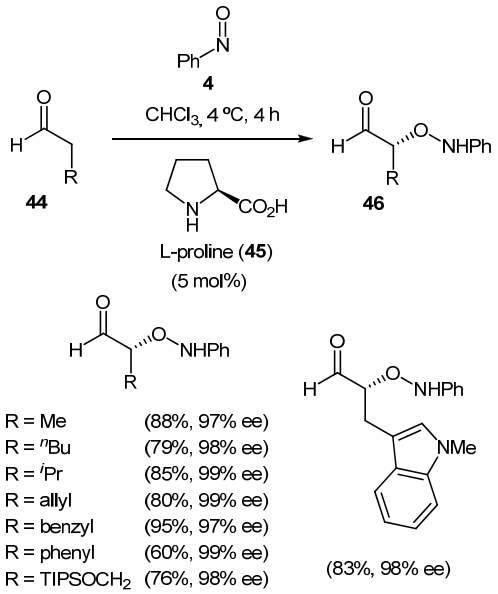
to give **43** as a mixture of isomers. The reaction was completely *N*-selective but low diastereoselectivites and moderate enantioselectivities were obtained (Scheme 10).



Scheme 10.

3. Organocatalyzed Reactions

The first enantioselective organocatalytic nitroso aldol reaction was described simultaneously by Zhong,[34] MacMillan[35] and Hayashi[36] in 2003. Condensation of nitrosobenzene **4** with aldehydes **44** in the presence of a catalytic amount of L-proline **45** afforded α- aminoxyaldehydes **46** in high yield and enantioselectivity (Scheme 11). Compounds **46** are oligomeric in solution and were most conveniently isolated as the corresponding primary alcohols after reduction with sodium borohydride. Considerable variation of bulkiness in substrates did not affect the enantiomeric excess. Notably, even though due to operational convenience the use of 5 mol% of catalyst ensure high efficiency, the reaction can be conducted with just 0.5 mol% of L-proline without substantial loss of enantiocontrol (18 h, 68%, 94% ee for R = Me).[35]



Scheme 11.

The enhanced Brønsted basicity of the nitrogen atom of L-proline was suggested to be the ultimate responsible for *O*-addition according to the model illustrated in Figure 2, corresponding to typical enamine catalysis.[34,35]

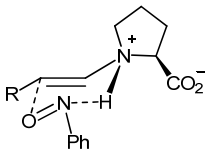


Figure 2. Model of addition for L-proline catalyzed nitroso aldol reaction with aldehydes

One year later, Córdova and co-workers reported the proline-catalyzed direct α-aminoxylation of different aliphatic ketones **47** (Table 6).[37,38] In the case of unsymmetrical ketones the reaction occurred exclusively on the methylene carbon. For acyclic ketones small amounts of the corresponding *N*-adducts were obtained (with the exception of allyl methyl ketone in which *N*-adduct was predominant) and only cyclohexanone showed to be completely *O*-selective. This result was simultaneously confirmed by Hayashi and co-workers[39] who also demonstrated that slow addition of nitrosobenzene made it unnecessary to use a large excess of ketone and only 2 equiv was enough. A further comprehensive study with cyclic six-membered ketones demonstrated that the reaction was completely *O*-selective for those substrates.[40] This study also showed a moderate diastereoselectivity with 3- or 4-substituted cyclohexanones that could lead to mixtures of isomers. In all cases, however, *O*-

selectivity and excellent enantioselectivity were maintained. Interestingly, *trans*-4-*tert*-butyldimethylsiloxy-L-proline **48** displayed a greater catalytic activity when compared with L-proline (Table 6).[41] In fact, the reaction also proceeded with high enatioselectivities (up to 96-99% ee) with *trans*-4-hydroxy-L-proline immobilized onto Merrifield-type resins. In general, reaction rates for cyclic six-membered ketones were higher for the immobilized catalyst **49** than those reported for L-proline.[42] Compound **50** derived from isosteviol has also been checked as a catalyst but enantioselectivities were lower than other catalysts in the case of aldehydes; however, higher ee value was obtained with cyclohexanone.[43]

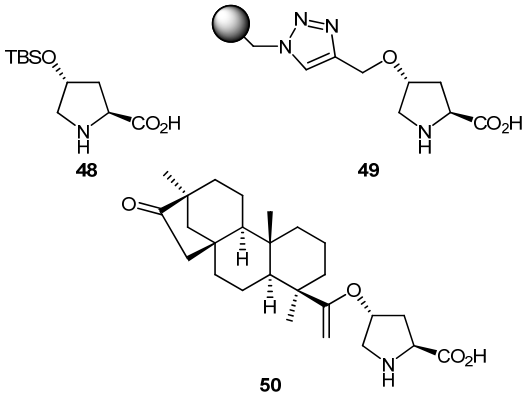
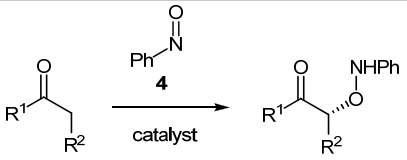


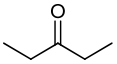
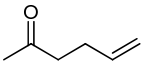
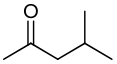
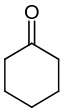
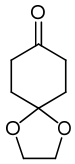
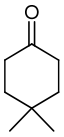
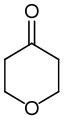
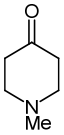
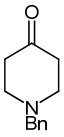
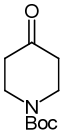
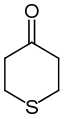
Figure 3. 4-substituted L-prolines

The same transition sate model operates for the reaction of both aldehydes and ketones. Simple DFT calculations made with ketones supported the same model illustrated in Figure 2 for aldehydes.[38] Non-linear effects were not observed so, quite likely a single proline molecule is involved in the mechanism. Houk and Cheong demonstrated that proline catalysis takes place via enamine attack on the oxygen of the nitrosobenzene monomer, following a similar model to that illustrated in Figure 2, but with a simultaneous proton transfer from the carboxylic acid.[44] Calculations with highly substituted *meso*-cyclohexanones, which underwent asymmetric desymmetrization through a nitroso aldol reaction catalyzed by L-proline,[45] demonstrated that the observed diastereoselectivity is due to the polar groups at γ-position of the ketone and to differences in conformations.[46]

Table 6 Nitroso Aldol Reaction of ketones catalyzed by L-proline derivatives[a]

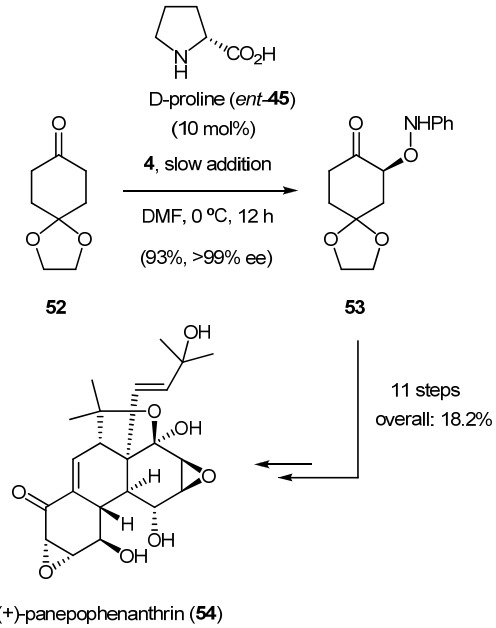


47 **51**

46	**Cat**	Cat. mol%	solvent	T (ºC)	t (h)	yield (%)	O/N	ee % of **50**	Ref.
	**45**	20	DMSO	rt	2-3	93	81:19	>99	[37]
	45	10	DMF	0	2	73	55:45	>99	[39]
	**45**	20	DMSO	rt	2-3	66	98:2	99	[37]
	48	10	DMF	0	1	50	1:0	>99	[41]
	**45**	20	DMSO	rt	2-3	87	8:22	>99	[37]
	**45**	20	DMSO	rt	2-3	64	90:10	>99	[37]
	45	20	DMSO	rt	2-3	70	>100:1	>99	[37]
	**45**	30	DMF	0	5.5	79	1:0	>99	[39]
	45	10	DMF	0	5.5	77	1:0	>99	[39]
	48	10	DMF	0	0.25	76	1:0	>99	[41]
	49	20	DMF	23	3	74	1:0	98	[42]
	50	10	buffer[b]	rt	0.07	87	1:0	>99	[43]
	**45**	20	DMSO	rt	2-3	99	1:0	>99	[38]
	45	30	DMF	0	12	96	1:0	>99	[39]
	45	10	DMF	0	24	93	1:0	>99	[39]
	45	5	DMF	0	60	86	1:0	>99	[39]
	49	20	DMF	23	3	75	1:0	99	[42]
	**45**	10	DMF	0	24	84	1:0	>99	[39]
	48	10	DMF	0	2	74	1:0	>99	[41]
	49	20	DMF	23	3	67	1:0	98	[42]
	**45**	10	DMF	0	24	53	1:0	96	[39]
	49	20	DMF	23	3	61	1:0	97	[42]
	**45**	10	DMF	0	24	44	1:0	99	[39]
	49	20	DMF	23	3	49	1:0	99	[42]
	**45**	10	DMF	0	60	45	1:0	>99	[40]
	**45**	10	DMF	0	24	41	1:0	>99	[40]
	**45**	10	DMF	0	25	69	1:0	>99	[40]
	48	10	DMF	0	2	68	1:0	>99	[41]

[a] Reactions were conducted with 1 equiv of nitrosobenzene and either 10 equiv (Ref. [37]) or 2 equiv (Ref.39, 41, 42 and 40) of ketone. [b] phosphate buffer pH = 9.1

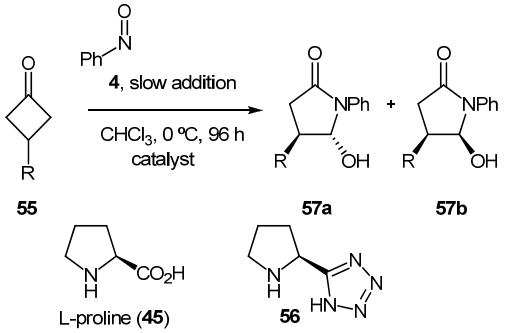
The synthetic utility of the reaction has been demonstrated by preparing (+)-panepophenanthrin **54** from adduct **53** -obtained using D-proline as a catalyst- in 11 steps and 18.2% overall yield (Scheme 12).[47]



Scheme 12

Four-membered cyclic ketones, i.e. cyclobutanones presented an unexpected behaviour when reacted with nitrosobenzene in the presence of L-proline. 3-Substitued cyclobutanones **55** underwent enantioselective desymmetrization to give 5-hydroxy-γ-lactams **57** instead of expected α-aminoxylated adduct; similar results were obtained when pyrrolidinyl tetrazol **56** was used as a catalyst (Table 7).[48]

Table 7 Desymmetrization of 3-substituted cyclobutanones[a]

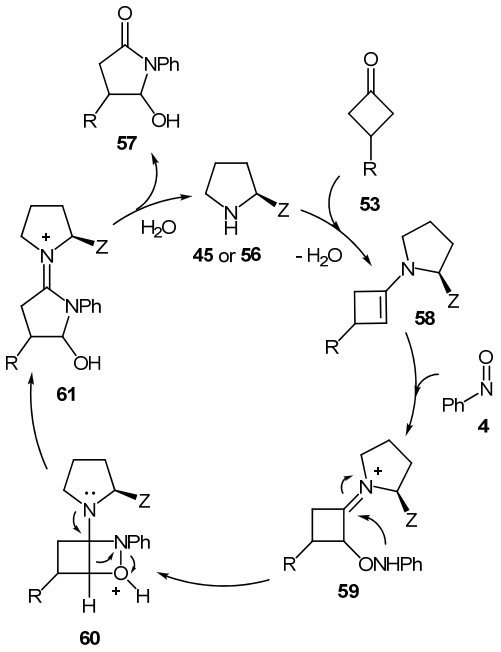


R	reaction conditions[a]	yield (%)	**55a**:**55b**	ee % of **55a**
Ph	A	40	95:5	20
	B	45	79:21	30
4-BrC_6H_4	A	57	73:27	27
	B	20	>99:1	4
4-MeC_6H_4	A	30	77:23	40
$PhCH_2CH_2$	A	65	93:7	51
	B	40	94:6	42
C_6H_{13}	A	60	67:33	38
	B	40	99:1	60

cyclohexyl	A	48	85:15	37
	B	41	72:28	56

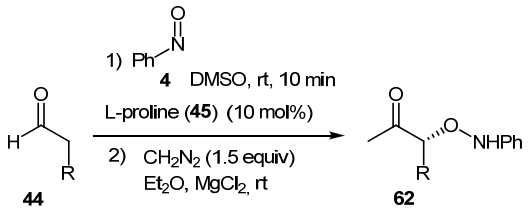
[a] Conditions A: 5.0 equiv of cyclobutanone, 1.0 equiv of nitrosobenzene and 30 mol% of **45**. Conditions B: 1.0 equiv of cyclobutanone, 3.0 equiv of nitrosobenzene and 20 mol% of **56**.

In general, good *trans*-selectivities were observed but moderate yields and enantioselectivities were obtained. The proposed mechanism for the observed ring expansion of compounds **53** is illustrated in Scheme 12. After initial α-oxyamination of the enamine **56** formed from **53**, the iminium intermediate **57** undergoes an intramolecular attack leading to bicycle **58** that rearranges into iminium **59**, which regenerates the catalyst after releasing the product.



Scheme 12

Asymmetric synthesis of 3-hydroxy-2-alkanones **62** was achieved through a tandem *O*-selective nitroso aldol reaction of aldehydes followed by subsequent chemoselective homologation with diazomethane (Scheme 13).[49] The reaction proceeded with moderate yields and excellent enantioselectivities.

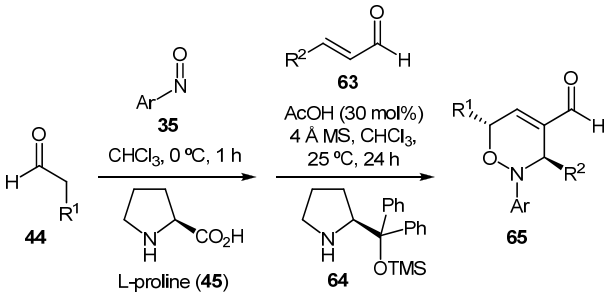


R = Me	(40%, 97% ee)	R = 4-$BrC_6H_4CH_2$	(57%, 98% ee)
R = $^nC_5H_{11}$	(46%, 98% ee)	R = $MeSCH_2$	(43%, 97% ee)
R = $^nC_{10}H_{21}$	(46%, 98% ee)	R = $TBSOCH_2CH_2$	(42%, 99% ee)
R = ^{i}Pr	(55%, 98% ee)	R = $BnOCH_2CH_2$	(41%, 95% ee)
R = benzyl	(60%, 97% ee)		

Scheme 13

Optically active 1,2-oxazines **65** were prepared in good chemical yields and excellent diastereo- and enantioselectivities through a dual-organocatalyzed asymmetric α-aminoxylation/aza-Michael/aldol condensation cascade (Table 8).[50]

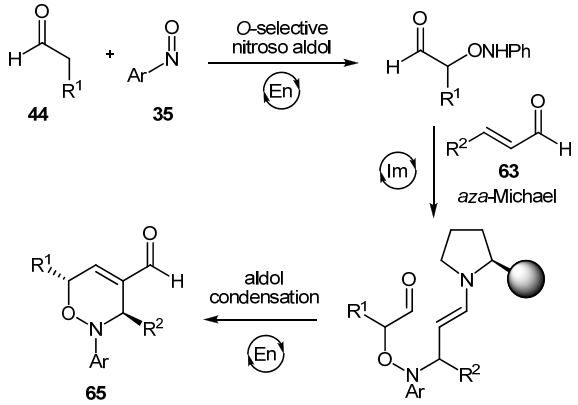
Table 8 α-aminoxylation/aza-Michael/aldol condensation cascade[a]



R^1	R^2	Ar	yield (%)	dr	ee %
Me	^{n}Pr	Ph	44	96:4	>99
Et	^{n}Pr	Ph	62	96:4	>99
^{i}Pr	^{n}Pr	Ph	58	97:3	>99
^{n}C7H15	^{n}Pr	Ph	51	95:5	>99
TsOC3H6	^{n}Pr	Ph	33	98:2	>99
^{i}Pr	^{n}Pr	4-BrC_6H_4	60	96:4	>99
^{i}Pr	^{n}Pr	4-$MeOC_6H_4$	59	>99:1	>99
^{i}Pr	^{n}Pr	4-ClC_6H_4	62	96:4	>99
^{i}Pr	Et	Ph	35	96:4	>99
^{i}Pr	^{n}C7H15	Ph	50	95:5	>99
^{i}Pr	CO_2Et	Ph	70	>99:1	>99
Et	CO_2Et	Ph	54	>99:1	>99
^{i}Pr	4-$CF_3C_6H_4$	Ph	37	>99:1	>99

[a] Reactions were conducted with 1 equiv of nitrosobenzene, 3 equiv of aldehyde **44** and 5 equiv of aldehyde **61**.

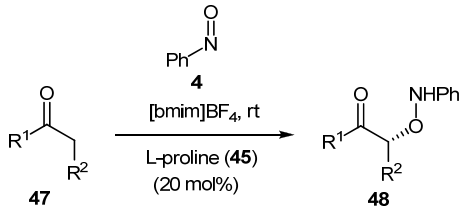
The general scheme for the cascade reaction is depicted in Scheme 14. Two organocatalysts were used in a one-pot procedure since L-proline was showed to be ineffective as the iminium catalyst required for the second step of the reaction. The loading of catalyst **64** was resized to 30 mol% in order to accelerate the *aza*-Michael reaction.

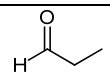
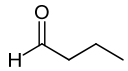
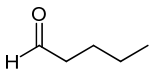
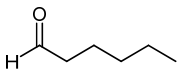
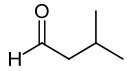
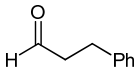
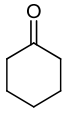


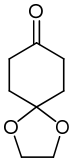
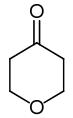
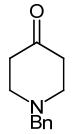
Scheme 14

In two simultaneous papers Wang[51] and Huang reported proline-catalyzed direct asymmetric α-aminoxylation of aldehydes and ketones using ionic liquid 1-n-butyl-3-methylimidazolium tetrafluoroborate as a solvent. The reaction was totally *O*-selective and proceeded with high yields and enantioselectivities (Table 9). Interestingly, the ionic liquid containing the catalyst was reused four[51] and six[52] times without substantial loss of efficiency.

Table 9 α-Aminoxylation reaction of aldehydes and ketones in ionic liquid[a]

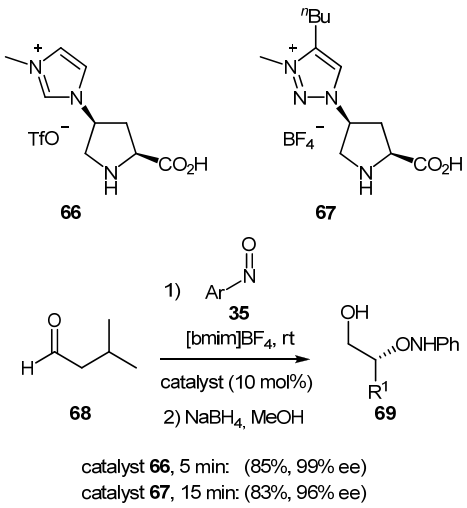


47	t (min)	yield[b] (%)	ee %	Ref.
	120	89	97	51
	10	94	99	52
	120	98	99	51
	10	89	98	52
	10	84	97	52
	120	76	99	51
	10	79	95	52
	120	91	98	51
	10	93	>99	52
	120	93	97	51
	10	85	>99	52
	120	67	>99	51
	120	74	>99	51
	15	89	>99	52

	120	70	>99	[51]
	15	85	99	[52]
	30	68	>99	[52]

[a] Reactions were conducted with 1 equiv of nitrosobenzene and 3 equiv (Ref. [51]) or 2 equiv (Ref.[52]) of aldehyde or 3 equiv (Ref. [51] and [52]) of ketone. b Isolated yield (in the case of aldehydes of the alcohol after reduction with sodium borohydride)

Proline was also incorporated covalently to the ionic liquid by preparing imidazolium ion-tagged prolines **66**[53] and **67**.[54] As an example the α-aminoxylation of 3-methylbutanal **68** in a ionic liquid as a solvent afforded, after *in situ* reduction, the corresponding diol **69** in good yield and high enantioselectivity for both catalysts (Scheme 15). The reaction catalyzed by **66** was also reported for cyclic six-membered ketones 99% ee being obtained. Catalyst **66** was reused up to seven times in the α-aminoxylation of cyclohexanone and >99% ee was obtained in all runs.[53]



Scheme 15

The addition of urea **70**[55] and thioureas **71** and **72**[56] (Figure 4) as co-catalysts to the nitroso aldol reaction catalyzed by L-proline resulted in higher reaction rates in more benign solvents.

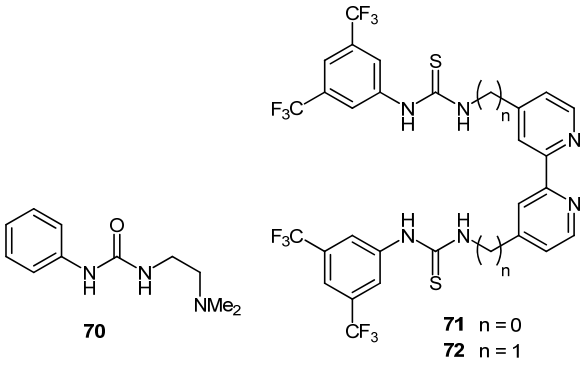
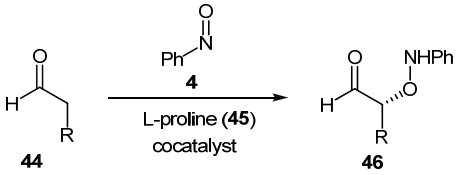


Figure 4. Co-catalysts for the proline-catalyzed α-Aminoxylation reaction of aldehydes

O-Selectivity as well as high yields and enantioselectivities are maintained (Table 10). Additional experiments including comparison with immobilized L-proline and soluble *trans*-4-(tertbutyldimethylsiloxy)-L-proline demonstrated that the role of urea **70** is not to facilitate the dissolution of the catalyst.[55] In agreement with the observations derived from those studies it has been suggested that co-catalyst **70** promotes enamine formation by interacting with an intermediate productive catalytic oxazolidinone. On the other hand, compounds **71** and **72** have been suggested[56] to promote favorable H-bond interactions in the transition state of the reaction between the carboxyl group of the catalyst and the NH groups of the bisthiourea

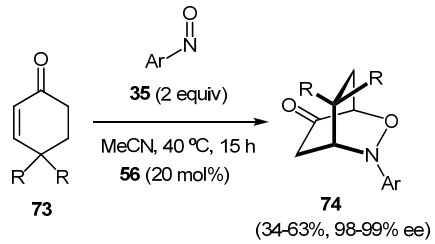
Table 10 Proline-catalyzed α-Aminoxylation reaction of aldehydes using cocatalysts[a]



R	cocatalyst	solvent	T (ºC)	t (h)	yield[b] (%)	ee %	Ref.
Me	**70**	EtOAc	0	2	96	99	[55]
	71	toluene	rt	6	85	99	[56]
	72	toluene	rt	6	67	98	[56]
Et	**71**	toluene	rt	6	76	98	[56]
	72	toluene	rt	6	60	97	[56]
^{n}Pr	**71**	toluene	rt	6	62	98	[56]
	72	toluene	rt	6	50	96	[56]
^{i}Pr	**70**	EtOAc	0	3	90	98	[55]
	71	toluene	rt	6	60	94	[56]
	72	toluene	rt	6	52	97	[56]
^{n}Bu	**70**	EtOAc	0	3.5	97	99	[55]
^{n}Hex	**70**	EtOAc	0	5	84	99	[55]
benzyl	**70**	EtOAc	0	3.5	84	>99	[55]
Ph	**70**	EtOAc	0	2	55	99	[55]
allyl	**70**	EtOAc	0	2.5	75	99	[55]

[a] Reactions were conducted with 1 equiv of nitrosobenzene and 3 equiv (Ref. [55]) or 2 equiv (Ref. [56]) of aldehyde. Catalyst and co-catalyst were added in 5 mol% (Ref. [55]) or 10 mol% (Ref. [56]). [b] Isolated yield of the alcohol after reduction with sodium borohydride

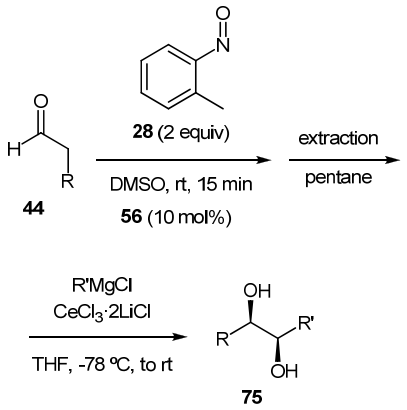
In addition to proline, other pyrrolidine-derived organocatalysts can be employed to catalyze an *O*-selective nitroso aldol reaction of aldehydes and ketones, the most used being pyrrolidinyl tetrazole **56** which showed excellent selectivity results rather similar to proline.[57] When 2-nitrosotoluene was employed in combination with **56** the addition time of the nitroso compound is greatly reduced in comparison with that for proline-catalyzed reactions thus avoiding the use of excess ketone.[58] Compound **56** has also been used successfully in the asymmetric desymmetrization of highly substituted *meso*-cyclic ketones through tandem aminoxylation/O-N bond heterolysis reactions.[45] Catalyst **56** has been employed in tandem processes involving *O*-selective nitroso aldol reactions. Tandem *O*-nitroso aldol / Michael reaction was reported by Yamamoto and co-workers with α,β-unsaturated cyclic ketones **73** (Scheme 16). [59] The methodology was applicable to various aromatic nitroso compounds. In a similar way to that observed for the direct α-aminoxylation (see above) higher catalytic activity was observed with *trans*-4-*tert*-Butyldimethylsiloxy-l-proline **48** when compared with both **56** and L-proline **45**. [41] The observed regioselectivity and the mechanism of the reaction was studied by DFT methods.[60] Calculations showed that the *O*-selective channel was much more energetically favorable then the *N*-selective channel. Both transition states corresponding to nitroso aldol and subsequent Michael addition had very similar barriers (5.37 and 5.43 kcal/mol, respectively).



Scheme 16

A sequential *O*-nitroso aldol and Grignard addition process catalyzed by **56** allowed the preparation of 1,2-diols in high diastereo- and enantioselectivities.[61] The process was made sequentially and the presence of benzoic acid was required in the first step for facilitating enamine formation. Since DMSO was showed to be more adequate for the nitroso aldol reaction but not suitable for the Grignard reaction, it was necessary to make an intermediate extraction with pentane to use the product for the next reaction

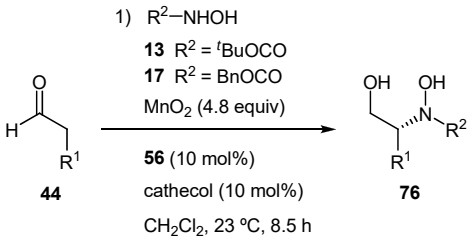
without any purification (Scheme 17). The N-O bond was cleaved by the organometallic reagent and the presence of the *ate* complex of $CeCl_3 \cdot 2LiCl$ was crucial for the high yields and selectivities. Similar results were obtaine dwith L-proline as catalyst. In some cases the use of organolithium R'Li derivatives increased the chemical yield.

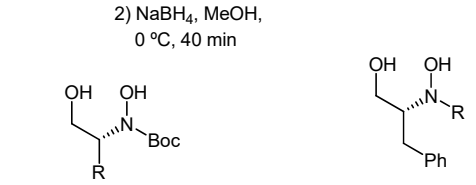


R = ^{i}Pr	R = Me	(63%, dr 93:7, 97% ee)
R = ^{i}Pr	R = Et	(62%, dr 95:5, 96% ee)
R = ^{i}Pr	R = allyl	(73%, dr 91:9, 96% ee)
R = ^{i}Pr	R = benzyl	(77%, dr >99:1, >99% ee)
R = ^{i}Pr	R = ^{i}Pr	(75%, dr 95:5, 98% ee)
R = ^{i}Pr	R = ^{t}Bu	(24%, dr >99:1, 97% ee)
R = ^{i}Pr	R = Ph	(65%, dr >99:1, 96% ee)
R = ^{i}Pr	R = 4-FC_6H_4	(74%, dr 95:5, 96% ee)
R = ^{i}Pr	R = 4-$MeOC_6H_4$	(71%, dr 96:4, 97% ee)
R = ^{i}Pr	R = 2-furyl	(65%, dr 94:6, 97% ee)
R = ^{i}Pr	R = $CH_2CO_2{}^t$Bu	(45%, dr 95:5, 93% ee)
R = Ph	R = Me	(66%, dr 93:7, 98% ee)
R = Ph	R = ^{n}Bu	(62%, dr 95:5, >99% ee)
R = Ph	R = allyl	(76%, dr 96:4, 99% ee)
R = Ph	R = benzyl	(72%, dr >99:1, >99% ee)
R = Ph	R = ^{i}Pr	(64%, dr >99:1, 98% ee)
R = Ph	R = ^{t}Bu	(57%, dr >99:1, >99% ee)
R = Ph	R = Ph	(61%, dr 96:4,98% ee)
R = allyl	R = allyl	(70%, dr 92:8, 98% ee)
R = allyl	R = benzyl	(65%, dr >99:1, 96% ee)
R = allyl	R = ^{i}Pr	(65%, dr 91:9, 96% ee)
R = allyl	R = Ph	(70%, dr 96:4, 98% ee)

Scheme 17

When the nitroso aldol reaction catalyzed by **56** was carried out in the presence of a Brønsted acid *N*-selectivity was predominant. Thus, the reaction between aldehydes and nitrosoformates generated *in situ* from the corresponding protected hydroxylamines **13** and **17** catalyzed by **56** and in the presence of cathecol resulted in an efficient method for accessing β-(hydroxyamino)alcohols **76** (Scheme 18).[62]



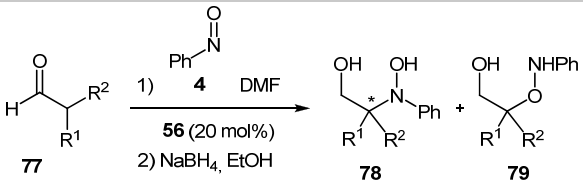


R = $PhCH_2$	(65%, 98% ee)	R = Cbz	(62%, 95% ee)
R = 4-$MeOC_6H_4CH_2$	(62%, 98% ee)	R = Fmoc	(48%, 91% ee)
R = 3-$ClC_6H_4CH_2$	(62%, 98% ee)	R = Et_3CO_2C	(52%, 94% ee)
R = *N*-Me-3-indolylCH_2	(58%, 95% ee)	R = AdO_2C	(41%, 97% ee)
R = Et	(62%, 92% ee)		
R = ^{i}Pr	(62%, 92% ee)		
R = ^{i}PrCH_2	(62%, 96% ee)		
R = cyclohexylCH_2	(62%, 95% ee)		
R = $^n C_6H_{13}$	(69%, 93% ee)		
R = Bn$O(CH_2)_3$	(61%, 95% ee)		
R = $Br(CH_2)_3$	(60%, 94% ee)		
R = Phth$N(CH_2)_3$	(69%, 94% ee)		
R = MeO_2CCH_2	(64%, 95% ee)		
R = allyl	(64%, 96% ee)		
R = $MeSCH_2$	(51%, 94% ee)		

Scheme 18.

In the case of α-branched aldehydes **77** the reaction with nitrosobenzene catalyzed by **56** afforded mixtures of *N*- and *O*-adducts with predominance of the former (Table 11).[63] The enantioselectivites were moderate for *N*-adducts **78** and low for *O*-adducts **79**.

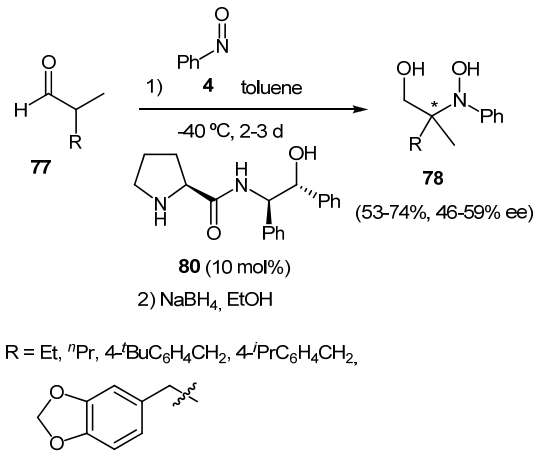
Table 11 Nitroso aldol reaction of α-branched aldehydes[a]



R^1	R^2	t (h)	yield (%)	**78**:**79**	ee % of **78**	ee % of **79**
Me[b]	$PhCH_2$	3	96	1:1	81	37
Me[c]	4-$MeOC_6H_4CH_2$	8	75	1.7:1	90	35
Me[c]	4-$BrC_6H_4CH_2$	3	98	1.4:1	86	45
Me[b]	Ph	24	83	20:1	64	n.d.
Me[b]	4-$MeOC_6H_4$	24	65	10:1	45	n.d.
Me[c]	$BnOCH_2$	4	89	0.8:1	79	5
Me[b]	allyl	3	91	0.7:1	62	27
Me[b]	Et	12	76	1.7:1	70	8
Et[b]	$PhCH_2$	6	67	1.3:1	25	11
Et[b]	^{n}Bu	12	55	0.6:1	5	2

[a] Reactions were conducted with 1 equiv of nitrosobenzene and 2 equiv of aldehyde. [b] Reaction carried out at 25 ºC. c Reaction carried out at 0ºC

Complete *N*-selectivity with α-branched aldehydes **77** was achieved using prolinamide **80** as a catalyst (Scheme 19).[64] After 2-3 days of reaction modest values of enantioselectivity were obtained.



Scheme 19

Pyrrolidine sulfonamide **81** exhibited high enantioselectivities (>99% ee in all cases) in a variety of organic solvents including, DMSO, $CHCl_3$, DMF, THF, EtOAc and MeCN. The best results in terms of chemical yield were observed with DMSO which was selected for studying the scope of the reaction (Table 12).[65] One year later, Córdova and co-workers reported the use of pyrroldine sulfonamide **82** also in DMSO as a solvent (Table 11).[66] Catalyst **82** was also used for tandem *O*-nitroso aldol / Michael reaction previously reported by Yamamoto,[59] but lower yields (22-23%) than those described were obtained.

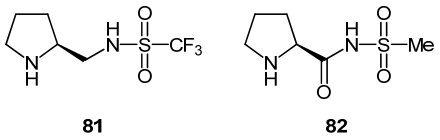
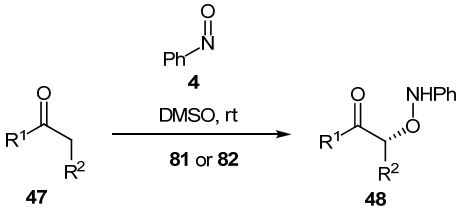
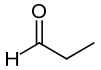
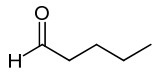
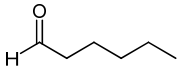
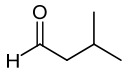
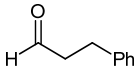
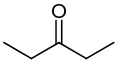
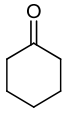
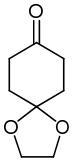
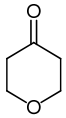
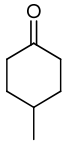


Figure 4. Pyrrolidine-sulfonamides

Table 12 α-Aminoxylation reaction of aldehydes and ketones catalyzed by pyrrolidine-sulfonamides[a]



47	cat.	t (h)	yield[b] (%)	ee %	Ref.
	**81**	0.3	66	>99	[65]
	82	2	66	>99	[66]

	**81**	0.3	73	>99	[65]
	**81**	0.3	74	>99	[65]
	**81**	0.3	81	>99	[65]
	**81**	0.3	79	>99	[65]
	**81**	0.3	71	97	[65]
	**81** **82**	0.3 2	84 80	>99 >99	[65] [66]
	**81** **82**	0.3 5	94 74	98 98	[65] [66]
	**81**	0.3	86	>99	[65]
	**82**	3	54	>99	[66]

[a] Reactions with catalyst **81** (20 mol%) were conducted with 2 equiv of nitrosobenzene and 1 equiv of aldehyde or ketone; reactions with catalyst **82** (10 mol%) were conducted with 1 equiv of nitrosobenzene and 2 equiv of aldehyde or ketone.

Maruoka and co-workers reported[67] the use of binaphthyl-derived secondary amine **83a** (Figure 5) as a suitable organocatalyst for nitroso aldol reactions. The reaction was completely *N*-selective and hydroxyaminated adducts **87** were obtained in high yields and enantioselectivities (Table12). On the other hand, aminoacid **84** and aminosulfonamide **85** promoted *O*-selective reactions.[68] Moreover, complementary induction of enantioselectivity was achieved with both **85** and **86**, which led to *R* and *S* diols **88**, respectively (Table 13). Higher enantiomeric excesses were observed for **88** which showed to be extremely efficient since it could be used at 0.2 mol%, the reaction going to completion in 8 hours with the same enantioselectivity. Those organocatalysts represent the first example of *O*-nitroso aldol reactions with a non-pyrrolidine derived organocatalyst. Interestingly, the same sense of enantioselectivity was observed for both catalysts with cyclohexanone. Whereas **85** led to the *R* enantiomer (63%, 99% ee), catalyst **86** furnished the *S* enantiomer although with lower enantioselectivity (71%, 74% ee)

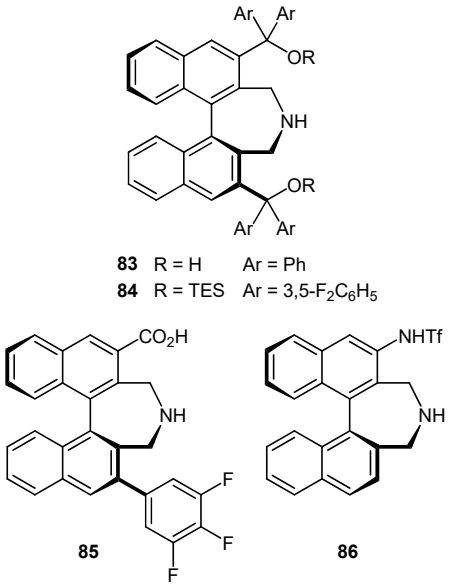
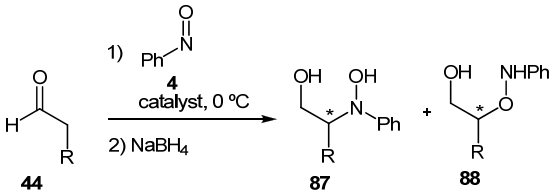


Figure 5. Binaphthyl-derived organocatalysts

Table 13 Complementary α-Aminoxylation reaction of aldehydes catalyzed by binaphthyl-derived catalysts[a]



R	cat.[b]	t (h)	yield[b] (%)	product	ee %	Ref.
Me	**83**	1	90	**87**	99 (*S*)	67
	85	1	89	**88**	86 (*R*)	68
	86	2	86	**88**	98 (*S*)	68
Et	**86**	2	90	**88**	97 (*S*)	68
^{n}Bu	**83**	1	76	**87**	96 (*S*)	67
	85	2	81	**88**	88 (*R*)	68
	86	2	92	**88**	98 (*S*)	68
benzyl	**83**	1	80	**87**	98 (*S*)	67
	85	3	75	**88**	59 (*R*)	68
	86	2	88	**88**	97 (*S*)	68
^{i}Pr	**83**	1	70	**87**	97 (*S*)	67
	85	1.5	69	**88**	86 (*R*)	68
	86	2	96	**88**	98 (*S*)	68
	86[c]	3	77	**88**	98 (*S*)	68
	86[d]	8	70	**88**	98 (*S*)	68
	86[d]	8	49	**88**	98 (*S*)	68
allyl	**86**	2	92	**88**	97 (*S*)	68
$BnOCH_2$	**86**	2	92	**88**	97 (*S*)	68
$CH_2{=}CH(CH_2)_7$	**83**	1	77	**87**	99 (*S*)	67
$^{c}C_6H_{11}CH_2$	**83**	1	86	**87**	99 (*S*)	67
$BnO(CH_2)_3$	**83**	1	86	**87**	97 (*S*)	67

[a] Reactions were conducted with 1 equiv of nitrosobenzene and 3 equiv of aldehyde. b Reactions catalyzed by **83** were carried out in THF using 10 mol% of catalyst and reactions catalyzed by **85** or **86** were carried out in $CHCl_3$ using 5 mol% of catalyst. [c] 1 mol% of catalyst was used. [d] 0.5 mol% of catalyst was used. [e] 0.2 mol% of catalyst was used.

From a mechanistic point of view, it was suggested that the each of hydroxydiphenylmethyl groups on **83** might play a different role.[67] Whereas one of them shields the *Re* face of the enamine, the other one directs and activates the *N*-addition through a H-bond with the oxygen atom of the nitroso compounds (Figure 6). By using catalysts **85** and **86** bearing more acidic groups, protonation of the nitrogen atom of the nitroso group should be favored thus promoting *O*-selective reactions.[68] Different transition states were suggested for the mode action of **85** and **86** (Figure 6). With compound **85** nitrosobenzene is activated and directed by the carboxyl group thus approaching the *Re* face of the *s-trans* enamine to give the *R* isomer. On the other hand, with compound **86** nitrosobenzene is activated by the distal acidic proton of the triflamide, approaching by the *Si* face of the *s-cis*-enamine, leading to *S* isomer.

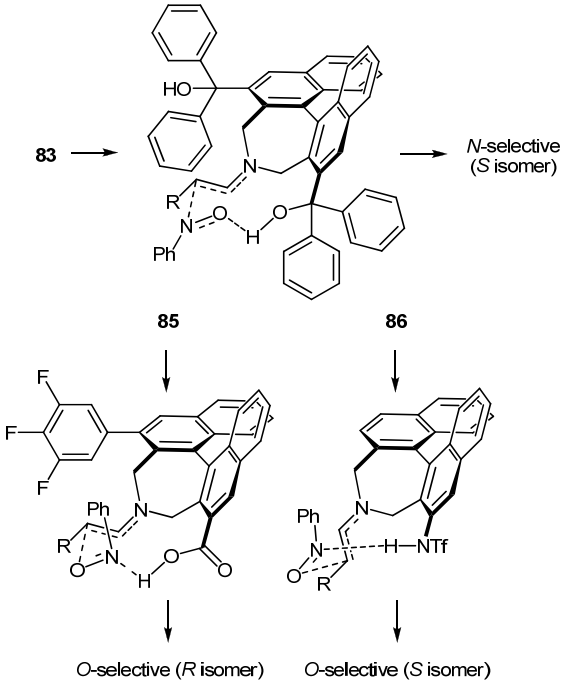
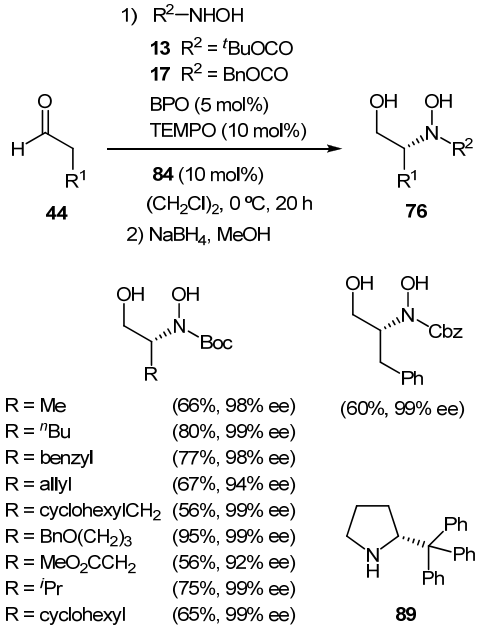


Figure 6. Transition states for catalysts **83**, **85** and **86**

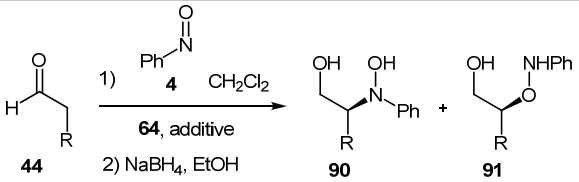
O-Silylated binhaphthyl derivative **84** catalyzed the addition of nitrosoformates to aldehydes (Scheme 20). [69] Complete *N*-selectivity was observed and the reaction proceeded with good yields and very high enantioselectivity. The oxidation *in situ* of the protected hydroxylamines **13** and **17**, precursors of nitrosoformates, was carried out with a mixture of benzoyl peroxide (BPO) and TEMPO. The same reaction was catalyzed by commercially available **89**.[70] Also in this case complete *N*-selectivity and enantioselectivity (99% ee) was achieved.



Scheme 20

Palomo and co-workers reported[71] that using commercially available **64** the nitroso aldol reaction with aldehydes could be completely regiocontrolled by the solely addition of an external Brønsted acid capable of protonating the nitrogen atom of the nitrosobenzene. The reaction of nitrosobenzene **4** with aldehydes **44** provided the corresponding *N*-adducts **90** in total regioselectivity and very high yields and enantioselectivities (Table 14). DFT calculations suggested that the reaction proceeds via an enol intermediate and not via an enamine intermediate.[72] On the other hand, when the reaction was carried out in the presence of 10 mol% of *p*-nitrobenzoic acid the corresponding *O*-adducts **91** were the only products obtained in the reaction.[73] In this case the enantioselective induction (giving rise to *S* enantiomers) was opposite to that observed for L-proline (promoting the formation of *R* enantiomers) and other pyrrolidine derivatives capable of promoting hydrogen transfer. In the case of compound **64** a classical steric model operates for the *O*-selective reaction and the attack of the nitroso compound takes place from the opposite face to the bulky group - $C(Ph_2)OTMS$.

Table 14 Regiocontrolled nitroso aldol reaction of aldehydes[a]

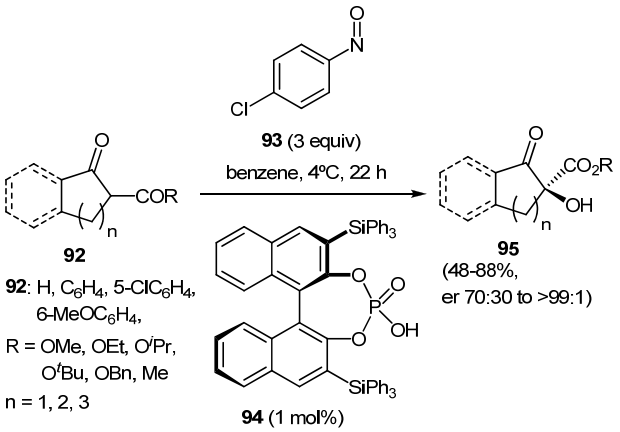


R	Cat mol%	additive[b]	t	T (ºC)	yield (%)	**90:91**	ee %	Ref.
Me	20	none	5 min	rt	70	>99:1	94	71
Et	20	none	5 min	rt	65	>99:1	99	71
^{n}Pr	20	none	10 min	0	60	>99:1	96	71
	20	none	30 min	-20	66	>99:1	98	71
	10	*p*-NO_2CO_2H	2 h	-20	78	0:1	>99	73
	5	*p*-NO_2CO_2H	16 h	-20	71	0:1	>99	73
$^{n}C_5H_{11}$	20	none	16 h	-20	74[c]	>99:1	98	71
$^{n}C_6H_{13}$	20	none	16 h	-20	75[c]	>99:1	98	71
	20	none	5 min	rt	42	>99:1	n.d.	71
^{n}Bu	10	*p*-NO_2CO_2H	2 h	-20	81	0:1	>99	73
benzyl	20	none	5 min	0	70	>99:1	94	71
	10	*p*-NO_2CO_2H	5 h	-20	68	0:1	>99	73
	5	*p*-NO_2CO_2H	16 h	-20	68	0:1	>99	73
^{i}Pr	20	none	30 min	0	60	>99:1	99	71
	10	*p*-NO_2CO_2H	2 h	-20	55	0:1	>99	73
	20	*p*-NO_2CO_2H	3 h	-20	59	0:1	>99	73
$BnOCH_2$	10	*p*-NO_2CO_2H	16 h	-20	45	0:1	>99	73
$BocHN(CH_2)_4$	10	*p*-NO_2CO_2H	3 h	-20	88	0:1	>99	73
$CH_2=CH(CH_3)_2$	10	*p*-NO_2CO_2H	4 h	-20	66	0:1	>99	73
2-$MeOC_6H_4CH_2$	20	none	5 min	0	40	>99:1	91	71

[a] Reactions were conducted with 1 equiv of nitrosobenzene and 3 equiv of aldehyde. [b] *p*-nitrobenzoic acid was used in 10 mol%. [c] reaction carried out in THF as a solvent

According to DFT calculations[73] the ultimate reason for the different regioselectivity observed in the presence of a Brønsted acid is a considerable lower energy barrier in the case of protonated nitrosobenzene (from 21.4 kcal/mol in the absence of any additive to 1.3 kcal/mol in the presence of *p*-nitrobenzoic acid).

Zhong and co-workers reported[74] the first chiral phosphoric acid-catalyzed α-hydroxylation of β-dicarbonyl compounds **92** through a tandem α-aminoxylation/N-O bond heterolysis sequence (Scheme 21). The reaction was carried out with 4-chloronitrosobenzene which showed better enantiocontrol than nitrosobenzene. Catalyst **94** could be used as low as 0.5 mol% without decrease in ee or O/N selectivity although for practical reasons it was preferred to be used in 1 mol%.



Scheme 21

Dimeric quinidine **96** (Figure 7) catalyzed enantioselective α-aminoxylation of oxindoles **34** to give 3-hydroxyindole derivatives **100** (Scheme 20). The reaction furnished quaternary centers at the C3 position of oxindoles in good yields and ee's.[75] On the other hand, cinchona-derived catalyst **97** showed exclusive *N*-selectivity furnishing the corresponding *N*-adducts **101** in good yields although moderate enantioselectivity.[76] The stereoselective induction of the electrophilic attack of the nitroso moiety was opposite by using catalysts **96** and **97**.

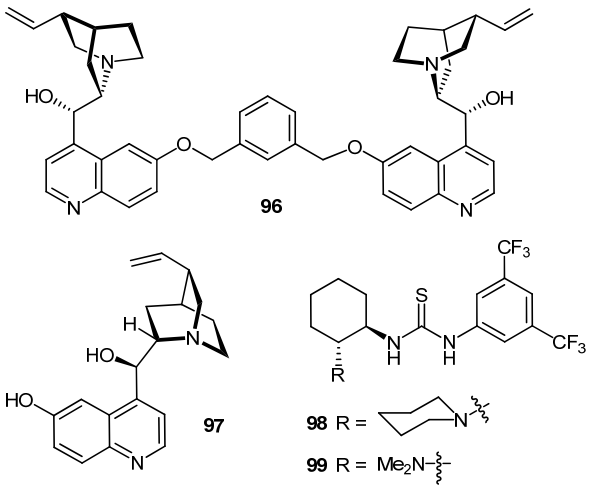
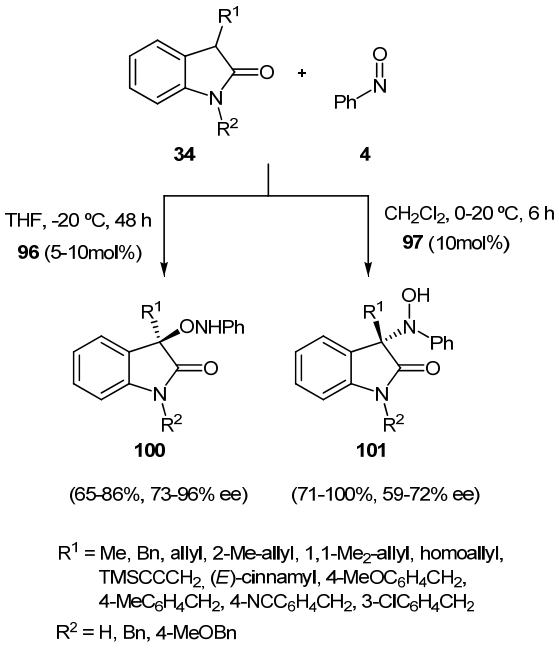
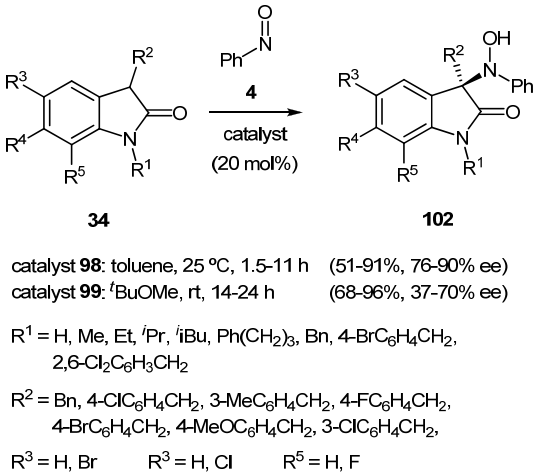


Figure 7. Organocatalysts used in nitroso aldol reactions of oxindoles



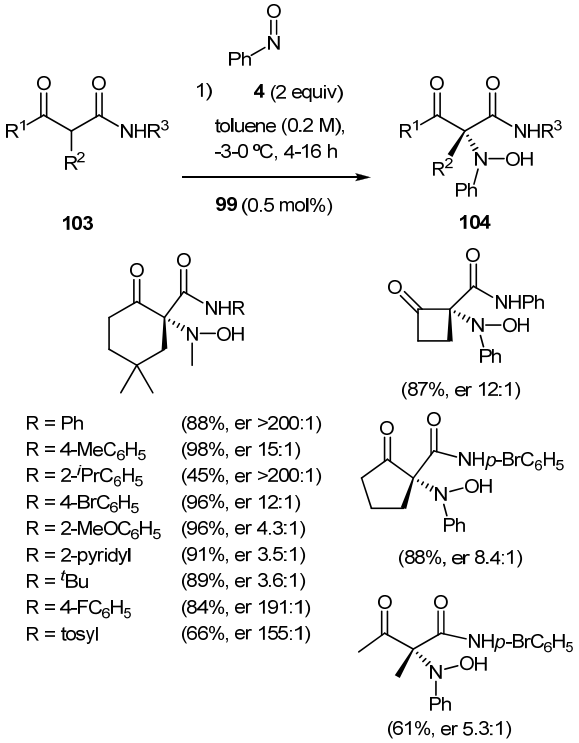
Scheme 22

Wang[77] and Moyano[78] simultaneously reported the asymmetric hydroxyamination of oxindoles catalyzed by bifunctional tertiary amine thioureas **98** and **99**, respectively. The same enantioselective induction was observed for both catalysts (contrary to that observed with **97**), compound **98** providing better results under standard isolation of the corresponding product. However, in the case of catalyst **99** gradual precipitation of the product was observed.[78] After collection of this solid by simple filtration when the reaction was complete it was observed that in all instances the enantiomeric purity of the precipitated product was much higher (up to 99% ee) than that resulting from the work up of the complete reaction crude (Scheme 23).



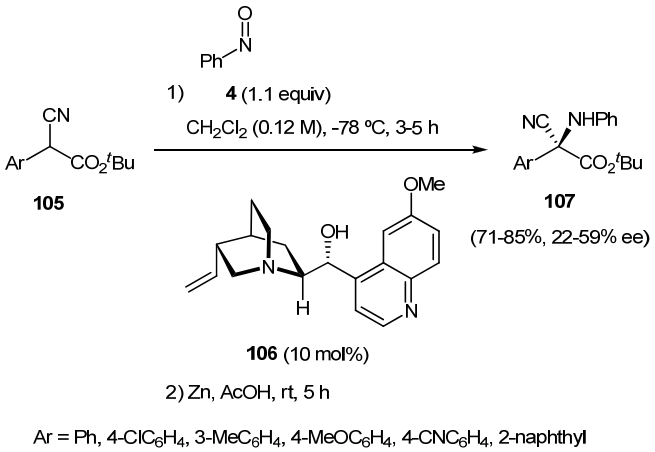
Scheme 23

Takemoto's thiourea **99** also catalyzed the α-hydroxyamination of β-ketoamides **103**. The reactions required a low catalyst loading (0.5 mol%) for obtaining high enantioselectivities (Scheme 24).[79]



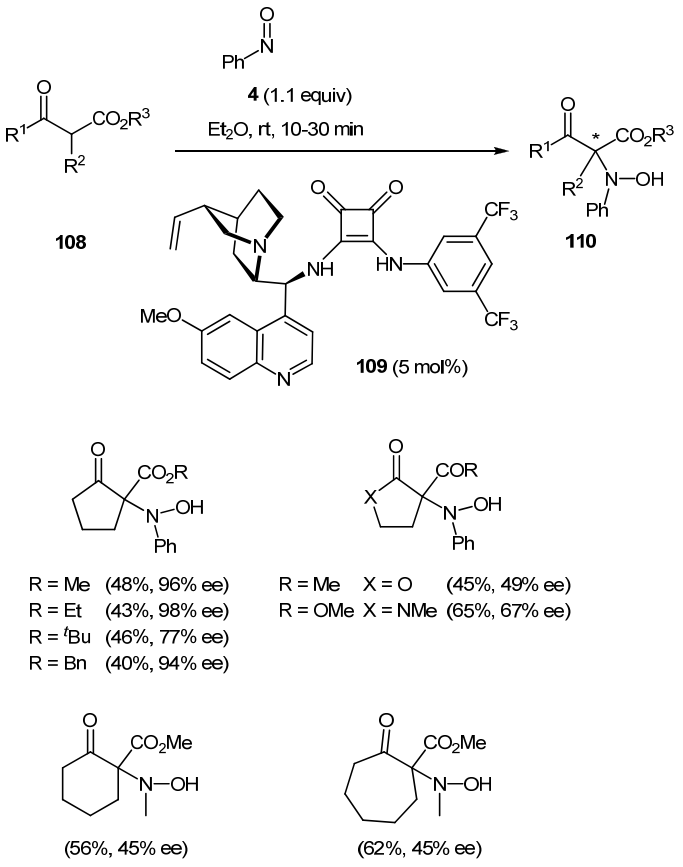
Scheme 24

Jørgensen and co-workers reported[80] the enantioselective nitroso aldol reaction between α-aryl-αcyanoacetates **105** and nitrosobenzene **4** catalyzed by quinine **106**. The *in situ* reduction with Zn in acetic acid afforded the corresponding α-aminonitriles **107** in high yield and moderate enantioselectivity (Scheme 24). An unusual effect on the enantioselectivity depending on both solvent and catalyst loading was observed.



Scheme 25

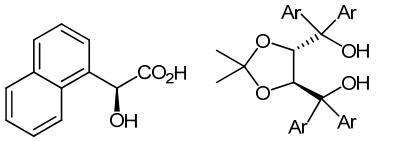
Cinchona squaramide bifunctional catalyst **109** catalyzed the nitroso aldol reaction between tertiary β-carbonyl esters **108** and nitrosobenzene.[81] The reaction proceeded rapidly in the presence of 5 mol% of catalyst to furnish compounds **110,** bearing a quaternary center, in moderate to good enantioselectivities (Scheme 25).



Scheme 26

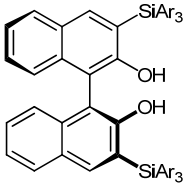
4. Enamine metal-free reactions

The nitroso aldol reaction catalyzed by a secondary amine is, actually, the reaction between an enamine and the nitroso compound in the rate-limiting step. Thus, it is possible to react directly an enamine with the nitroso derivative. If the reaction is made in the presence of a chiral catalyst the process becomes enantioselective. In 2005 Yamamoto reported[82] a totally regiocontrolled reaction between cyclic enamines and nitrosobenzene. Whereas the reaction catalyzed by glycocolic acid **111** (Figure 8) afforded *O*-nitroso aldol adducts **115**, by using TADDOL **112** as a catalyst, *N*-nitroso aldol products **116** were obtained (Table 15). With diol **113** complete *N*-selectivity was also observed.[83]



111

112 Ar = 1-naphthyll

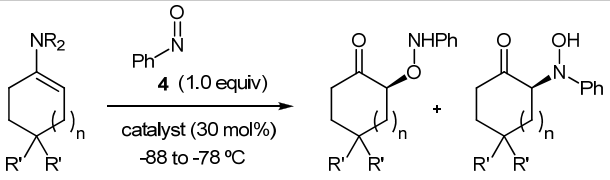


113 Ar = 3,5-xylyl

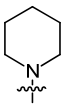
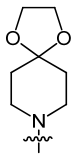
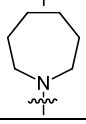
Figure 8. Catalysts for the reaction between enamines and nitroso compounds

The reaction outlined in Table 15 has been studied theoretically to rationalize the effect of the catalyst on the regio- and enantioselectivity[84] Whereas the enantioselectivity is exclusively due to steric factors, three key H-bond interactions must be considered for rationalizing the regioselectivity. These H-bonds are between the organic acid and i) the -N=O group, ii) the *ortho* hydrogen atom in PhNO and iii) the hydrogen atom of the NMe part of the enamine. A comparison between the strengths of the H-bonds and the energy levels of the transition structures allowed understanding the factors accounting for regioselectivity.

Table 15 Regiocontrolled nitroso aldol reaction of enamines[a]



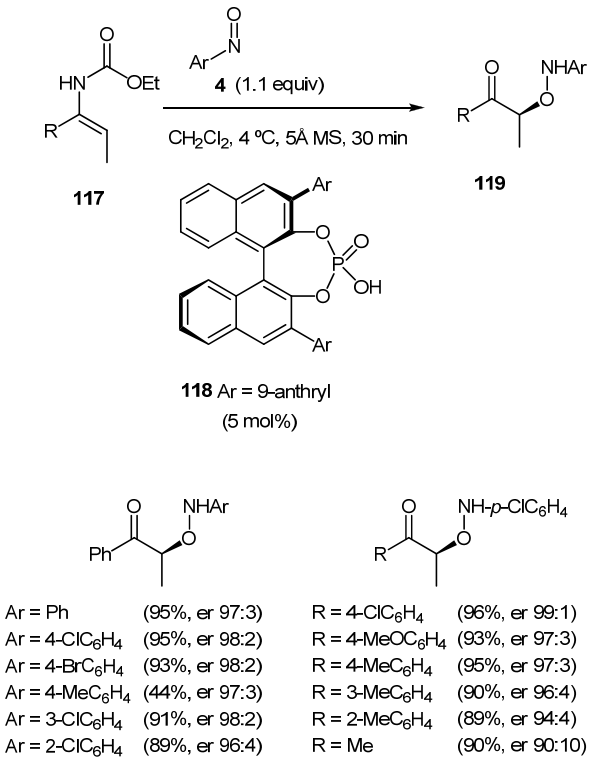
114 **115** **116**

NR_2	R'	n	cat.	prod.	yield (%)	ee %
	H	1	**111**	**115**	69	70
	H	0	**111**	**115**	63	70
			112	**116**	<1	---
	H	1	**111**	**115**	77	92
			112	**116**	81	83
	Me	1	**111**	**115**	91	90
			112	**116**	78	82
	$-(OCH_2)_2O-$	1	**111**	**115**	83	93
			112	**116**	63	91
	H	2	**111**	**115**	<1	---
			112	**116**	67	65
	H	1	**111**	**115**	89	91
			112	**116**	81	80
	H	1	**111**	**115**	64	83

[a] Reactions with catalyst **111** were carried out in diethyl ether for 12 h; reactions with catalyst **112** were carried out in toluene for 2 h

The enantioselective α-aminoxylation of enecarbamates **117**, an activated ketone nucleophile, was reported by Zhong and co-workers.[85] The presence of an electron-withdrawing carbamate group, instead of an electron-donating pyrrolidine moiety (in a typical enamine), avoid *N*-addition and only *O*-nitroso aldol adducts were obtained. The use of a strong Brønsted acid such as chiral phosphoric acid **118** favored protonation of the nitrogen atom of the nitroso compound, also directing the reaction towards *O*-

adducts (Scheme 26). Indeed, DFT calculations demonstrated that the path involving protonation of the nitrogen atom was favored by 2.91 kcal/mol over the path involving protonation of the oxygen atom.



Scheme 27

The reaction showed a good scope with a broad spectrum of nitrosoarenes and it could be extended to enecarbamates derived from indanones and tetralones giving rise to α-aminoxylated products in good yields (up to 91%) and enantiomeric ratios (up to 96:4). The synthetic utility of the transformation was demonstrated by converting compounds **119** into the corresponding protected β-amino alcohols.

5. Concluding Remarks

The combined effort of several research groups throughout the world leadered by that of Prof. Hisashi Yamamoto in USA have made major contribution to the area of nitroso chemistry and in particular to catalytic asymmetric nitroso aldol reaction. Both metal and organic catalysts have proved to be effective for achieving a complete regioselectivity and high enantioselectivities thus rendering the nitroso aldol reaction in

both *O*- and *N*-selective paths synthetically very useful. The development of efficient catalysts has required a delicate balance between the sterics and electronics of the chiral control elements around the nitroso compound. For instance, preferential H-bond interaction of either the nitrogen atom or the oxygen atom of the N=O group is crucial for the regioselectivity in organocatalytic reactions. In summary, several positive features for the catalytic asymmetric nitroso aldol reaction are worth of mention: i) The regioselectivity can be controlled completely using both metal and organic catalysis. ii) The substrate scope is broad including aldehydes, ketones, esters and amides. iii) Theoretically studied models allow rationalizing and predicting the regio- and stereochemical outcome of the reaction with a reasonable level of confidence. iv) Excellent levels of enantioselectivity are achieved with a variety of catalysts. v) The work-up of the reaction is easy and in many cases releasing of hydroxy and amino functionalities can be done *in situ* in a one-pot process. As a consequence, suitable methods for obtaining enantiomerically pure α-amino and α-hydroxy carbonyl compounds have been developed. Key challenges in this field lie in the further use of the nitroso aldol reaction in domino processes (only few examples are reported) and in the further optimization of the reactions already possible to other substrates including open-chain ketones and α-branched aldehydes and ketones.

Acknowledgments

References

1. Zuman, P.; Shah, B. *Chem. Rev.* **1994**, *94*, 1621-1641.
2. Lee, J.; Chen, L.; West, A. H.; RichterAddo, G. B. *Chem. Rev.* **2002**, *102*, 1019-1065.
3. Yamamoto, H.; Kawasaki, M. *Bull. Chem. Soc. Jpn.* **2007**, *80*, 595-607.
4. Yamamoto, H.; Momiyama, N. *Chem. Commun. (Cambridge, U. K.)* **2005**, 3514-3525.
5. Adam, W.; Krebs, O. *Chem. Rev.* **2003**, *103*, 4131-4146.
6. Baidya, M.; Yamamoto, H. *Synthesis* **2013**, *45*, 1931-1938.
7. Malkov, A. V. *Chem. Heterocycl. Compd.* **2012**, *48*, 39-43.
8. Yamamoto, Y.; Yamamoto, H. *Eur. J. Org. Chem.* **2006**, 2031-2043.
9. Bodnar, B. S.; Miller, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 5629-5646.
10. Leach, A. G.; Houk, K. N. *J. Chem. Soc., Chem. Commun.* **2002**, 1243-1255.
11. Streith, J.; Defoin, A. *Synthesis* **1994**, 1107-1117.
12. Sasaki, T.; Mori, K.; Ohno, M. *Synthesis* **1985**, 279-280.
13. Momiyama, N.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2002**, *41*, 2986-2988.
14. Morales, M. R.; Momiyama, N.; Yamamoto, H. *Synlett* **2006**, 705-708.
15. Momiyama, N.; Yamamoto, H. *Org. Lett.* **2002**, *4*, 3579-3582.

16. Merino, P.; Tejero, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 2995-2997.
17. Yu, C.; Song, A.; Zhang, F.; Wang, W. *ChemCatChem* **2014**, *6*, 1863-1865.
18. Palmer, L. I.; Frazier, C. P.; Alaniz, J. R. d. *Synthesis* **2013**, 269-280.
19. Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 6038-6039.
20. Kawasaki, M.; Li, P.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 3795-3797.
21. Yanagisawa, A.; Takeshita, S.; Izumi, Y.; Yoshida, K. *J. Am. Chem. Soc.* **2010**, *132*, 5328-5329.
22. Baidya, M.; Griffin, K. A.; Yamamoto, H. *J. Am. Chem. Soc.* **2012**, *134*, 18566-18569.
23. Frazier, C. P.; Sandoval, D.; Palmer, L. I.; Read de Alaniz, J. *Chem. Sci.* **2013**, *4*, 3857-3862.
24. Sandoval, D.; Frazier, C. P.; Bugarin, A.; Read de Alaniz, J. *J. Am. Chem. Soc.* **2012**, *134*, 18948-18951.
25. Maji, B.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 14472-14475.
26. Tian, G.-Q.; Yang, J.; Rosa-Perez, K. *Org. Lett.* **2010**, *12*, 5072-5074.
27. Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5360-5361.
28. Yanagisawa, A.; Izumi, Y.; Takeshita, S. *Synlett* **2009**, 716-719.
29. Yanagisawa, A.; Fujinami, T.; Oyokawa, Y.; Sugita, T.; Yoshida, K. *Org. Lett.* **2012**, *14*, 2434-2437.
30. Shen, K.; Liu, X.; Wang, G.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2011**, *50*, 4684-4688, S4684/4681-S4684/4659.
31. Maji, B.; Baidya, M.; Yamamoto, H. *Chem. Sci.* **2014**, *5*, 3941-3945.
32. Selig, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 7080-7082.
33. Xu, Y.-J.; Liu, Q.-Z.; Dong, L. *Synlett* **2007**, 273-277.
34. Zhong, G. *Angew. Chem. Int. Ed.* **2003**, *42*, 4247-4250.
35. Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808-10809.
36. Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293-8296.
37. Bogevig, A.; Sunden, H.; Cordova, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1109-1112.
38. Cordova, A.; Sunden, H.; Bogevig, A.; Johansson, M.; Himo, F. *Chem. - Eur. J.* **2004**, *10*, 3673-3684.
39. Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 1112-1115.
40. Hayashi, Y.; Yamaguchi, J.; Sumiya, T.; Hibino, K.; Shoji, M. *J. Org. Chem.* **2004**, *69*, 5966-5973.
41. Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Sumiya, T.; Urushima, T.; Shoji, M.; Hashizume, D.; Koshino, H. *Adv. Synth. Catal.* **2004**, *346*, 1435-1439.
42. Font, D.; Bastero, A.; Sayalero, S.; Jimeno, C.; Pericas, M. A. *Org. Lett.* **2007**, *9*, 1943-1946.
43. An, Y.-J.; Wang, C.-C.; Xu, Y.-Z.; Wang, W.-J.; Tao, J.-C. *Catal. Lett.* **2011**, *141*, 1123-1129.
44. Cheong, P. H.-Y.; Houk, K. N. *J. Am. Chem. Soc.* **2004**, *126*, 13912-13913.
45. Ramachary, D. B.; Barbas, C. F., III *Org. Lett.* **2005**, *7*, 1577-1580.
46. Joseph, J.; Ramachary, D. B.; Jemmis, E. D. *Org. Biomol. Chem.* **2006**, *4*, 2685-2689.
47. Matsuzawa, M.; Kakeya, H.; Yamaguchi, J.; Shoji, M.; Onose, R.; Osada, H.; Hayashi, Y. *Chem. - Asian J.* **2006**, *1*, 845-851.
48. Capitta, F.; Frongia, A.; Ollivier, J.; Piras, P. P.; Secci, F. *Synlett* **2011**, 89-93.
49. Yang, L.; Liu, R.-H.; Wang, B.; Weng, L.-L.; Zheng, H. *Tetrahedron Lett.* **2009**, *50*, 2628-2631.
50. Lin, H.; Tan, Y.; Sun, X.-W.; Lin, G.-Q. *Org. Lett.* **2012**, *14*, 3818-3821.
51. Guo, H.-M.; Niu, H.-Y.; Xue, M.-X.; Guo, Q.-X.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Wang, J.-J. *Green Chem.* **2006**, *8*, 682-684.
52. Huang, K.; Huang, Z.-Z.; Li, X.-L. *J. Org. Chem.* **2006**, *71*, 8320-8323.

53. Ding, X.; Tang, W.; Zhu, C.; Cheng, Y. *Adv. Synth. Catal.* **2010**, *352*, 108-112.
54. Khan, S. S.; Shah, J.; Liebscher, J. *Tetrahedron* **2011**, *67*, 1812-1820.
55. Poe, S. L.; Bogdan, A. R.; Mason, B. P.; Steinbacher, J. L.; Opalka, S. M.; McQuade, D. T. *J. Org. Chem.* **2009**, *74*, 1574-1580.
56. Demir, A. S.; Basceken, S. *Tetrahedron Asymmetry* **2013**, *24*, 1218-1224.
57. Momiyama, N.; Torii, H.; Saito, S.; Yamamoto, H. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5374-5378.
58. Jiao, P.; Yamamoto, H. *Synlett* **2009**, 2685-2687.
59. Yamamoto, Y.; Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 5962-5963.
60. Zhu, R.; Zhang, D.; Wu, J.; Liu, C. *J. Mol. Struct. THEOCHEM* **2007**, *815*, 105-109.
61. Jiao, P.; Kawasaki, M.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 3333-3336, S3333/3331-S3333/3342.
62. Maji, B.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 8714-8717.
63. Kim, S.-G.; Park, T.-H. *Tetrahedron Lett.* **2006**, *47*, 9067-9071.
64. Guo, H.-M.; Cheng, L.; Cun, L.-F.; Gong, L.-Z.; Mi, A.-Q.; Jiang, Y.-Z. *Chem. Commun. (Cambridge, U. K.)* **2006**, 429-431.
65. Wang, W.; Wang, J.; Li, H.; Liao, L. *Tetrahedron Lett.* **2004**, *45*, 7235-7238.
66. Sunden, H.; Dahlin, N.; Ibrahem, I.; Adolfsson, H.; Cordova, A. *Tetrahedron Lett.* **2005**, *46*, 3385-3389.
67. Kano, T.; Ueda, M.; Takai, J.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 6046-6047.
68. Kano, T.; Yamamoto, A.; Shirozu, F.; Maruoka, K. *Synthesis* **2009**, 1557-1563.
69. Kano, T.; Shirozu, F.; Maruoka, K. *J. Am. Chem. Soc.* **2013**, *135*, 18036-18039.
70. Kano, T.; Shirozu, F.; Maruoka, K. *Org. Lett.* **2014**, *16*, 1530-1532.
71. Palomo, C.; Vera, S.; Velilla, I.; Mielgo, A.; Gomez-Bengoa, E. *Angew. Chem. Int. Ed.* **2007**, *46*, 8054-8056.
72. Wong, C. T. *Tetrahedron Lett.* **2009**, *50*, 811-813.
73. Mielgo, A.; Velilla, I.; Gomez-Bengoa, E.; Palomo, C. *Chem. - Eur. J.* **2010**, *16*, 7496-7502, S7496/7491-S7496/7443.
74. Lu, M.; Zhu, D.; Lu, Y.; Zeng, X.; Tan, B.; Xu, Z.; Zhong, G. *J. Am. Chem. Soc.* **2009**, *131*, 4562-4563.
75. Bui, T.; Candeias, N. R.; Barbas, C. F. *J. Am. Chem. Soc.* **2010**, *132*, 5574-5575.
76. Zhang, T.; Cheng, L.; Liu, L.; Wang, D.; Chen, Y.-J. *Tetrahedron Asymmetry* **2010**, *21*, 2800-2806.
77. Jia, L.-N.; Huang, J.; Peng, L.; Wang, L.-L.; Bai, J.-F.; Tian, F.; He, G.-Y.; Xu, X.-Y.; Wang, L.-X. *Org. Biomol. Chem.* **2012**, *10*, 236-239.
78. Companyo, X.; Valero, G.; Pineda, O.; Calvet, T.; Font-Bardia, M.; Moyano, A.; Rios, R. *Org. Biomol. Chem.* **2012**, *10*, 431-439.
79. Mailhol, D.; Castillo, J.-C.; Mohanan, K.; Abonia, R.; Coquerel, Y.; Rodriguez, J. *ChemCatChem* **2013**, *5*, 1192-1199.
80. Lopez-Cantarero, J.; Cid, M. B.; Poulsen, T. B.; Bella, M.; Garcia Ruano, J. L.; Jorgensen, K. A. *J. Org. Chem.* **2007**, *72*, 7062-7065.
81. Yang, H.-J.; Dai, L.; Yang, S.-Q.; Chen, F.-E. *Synlett* **2012**, *23*, 948-950.
82. Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2005**, *127*, 1080-1081.
83. Momiyama, N.; Yamamoto, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 1190-1195.
84. Akakura, M.; Kawasaki, M.; Yamamoto, H. *Eur. J. Org. Chem.* **2008**, 4245-4249.
85. Lu, M.; Lu, Y.; Zhu, D.; Zeng, X.; Li, X.; Zhong, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 8588-8592, S8588/8581-S8588/8570.