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Advanced Synthesis & Catalysis

Enantioselective Catalyzed Synthesis of Amino Derivatives Using Electrophilic Open-Chain *N*-Activated Ketimines

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Abstract: *N*-Activated ketimines are characterized by the presence of acyl, sulfonyl, and phosphinoyl groups linked to the nitrogen atom of the azomethine system. These electron-withdrawing groups enhance the electrophilic character of the imino moiety allowing the addition of even weak nucleophilic reagents. The presence of the oxygen atoms in these activating groups with its coordinating and Lewis or Brønsted properties is of paramount importance in asymmetric catalyzed reactions. This review collects the results that have appeared in the literature during the last two decades on the utilization of open-chain *N*-activated ketimines for the synthesis of optically active α-disubstituted and α-trisubstituted amino derivatives including nitrogen-containing heterocyclic compounds.

Keywords: asymmetric synthesis; homogeneous catalysis; imines; nucleophilic addition; organocatalysis

1. Introduction

The enantioselective catalyzed addition of various nucleophilic reagents to azomethine systems is undoubtedly a straightforward approach to the synthesis of optically active amino derivatives.[1] Classical imines obtained by condensation of carbonyls with alkyl or aryl amines have been used for a long time as substrates for this purpose but they have increasingly being replaced by other imino derivatives endowed of a superior reactivity.[2] As a matter of fact, the introduction of electron-withdrawing substituents at the nitrogen atom of the imino moiety notably boosts the electrophilic character of the azomethine group allowing a fruitful addition even using mild nucleophilic reagents.[3] This aspect becomes of fundamental importance when ketimines having a lower reactivity over their aldimine counterparts are planned to be used for this purpose. In this context, ketimines are rather versatile substrates since their reaction with carbon

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centered nucleophiles easily provides access to quaternary carbon-containing amino derivatives. The α-trisubstituted amino motif is present in a notable number of biologically active compounds, including α,α-disubstituted amino acid derivatives. The construction of quaternary carbon-containing amino compounds is known to be a challenging task and thus efficient protocols allowing a stereocontrolled access to these frameworks are of particular synthetic interest.[4] Besides, 1,1-disubstituted primary amines can be obtained by stereocontrolled reduction of ketimines. The nature of the activating group linked to the nitrogen atom in these ketimines takes a crucial role since it should also act as a cleavable protecting group in the event that the free amino moiety is required. Thus, the electron-withdrawing effect of this group would be also flanked by a somewhat stability that warrants its persistence in the target amino derivative under various conditions. All over the years, the interest of researchers has mainly been focused on three ketimine derivatives which availability and reactivity in enantioselective catalyzed processes has been demonstrated particularly effective. Ketimines **1**–**3** can be considered as *N*-derivatives of different acid systems which are responsible for the electron-withdrawing effect on the nitrogen atom (Figure 1).

N-Acylketimines **1** are the most reactive compounds among *N*-activated ketimines and show a limited stability which sometimes poses some trouble concerning their preparation and storage.[5] Conversely, *N*-sulfonylketimines **2** and *N*-diarylphosphinoyl-ketimines **3** can be prepared directly from the corresponding ketones and show a relatively good stability which has dictated their success in these processes.[6] A fourth

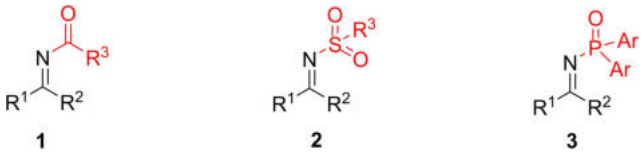


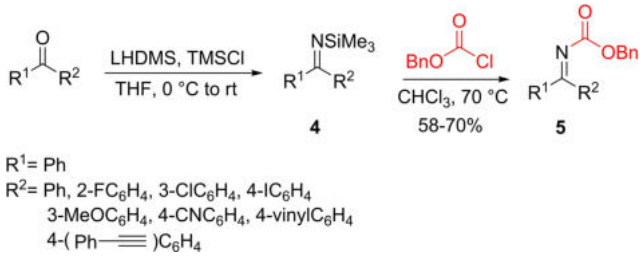
Figure 1. General structure of *N*-activated ketimines.

class of derivatives strictly related to **2** are *N*-arylsulfinylketimines bearing a stereogenic center on the sulfur atom.[7] The configurational stability of these compounds make them particularly effective in diastereoselective nucleophilic additions with a large array of reagents. These chiral ketimines will not be included in this review which is focused on asymmetric catalyzed processes using open-chain *N*-activated ketimines **1**–**3** appeared in literature during the last two decades. Asymmetric reactions on related ketimines obtained from cyclic ketones have not been largely practiced except those arising from isatins which have been recently reviewed.[8] Because of the tautomeric equilibrium existing between imines and the corresponding azaenols, direct involvement of these *N*-activated ketimines as nucleophilic reagents under basic conditions has been reported.[9] Since these examples belong to the domain of the wide reactivity of enamides with electrophilic substrates, this aspect is not pertinent to the present review and therefore it has been omitted.

2. Preparation of *N*-Activated Ketimines

2.1. *N*-Acylketimines

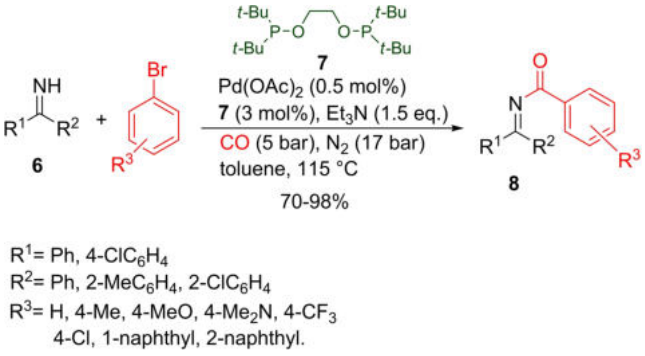
The direct synthesis of open-chain *N*-acylketimines by condensation of ketones and amides or carbamates is usually prevented by the unfavorable equilibrium of this process. A viable alternative for the preparation of *N*-carbamoylketimines **5** consists in the preliminary conversion of diaryl ketones into the corresponding *N*-trimethylsilylimines **4** which without purification, can be made to react with benzyl chloroformate leading to ketimines **5** (Scheme 1).[10]



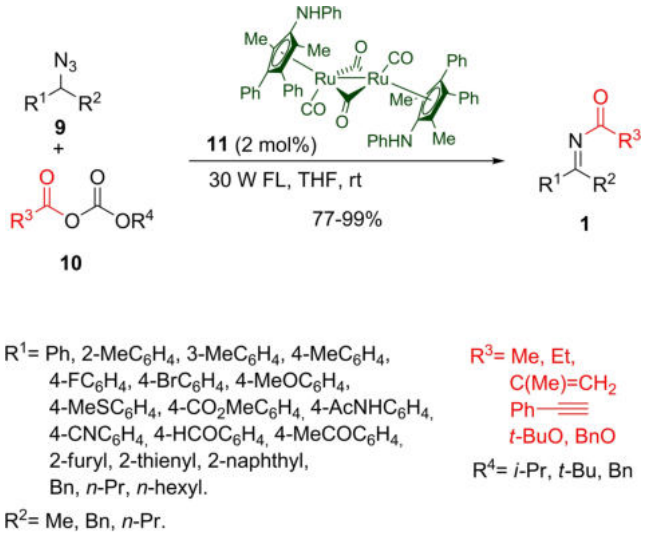
Scheme 1. Synthesis of *N*-benzyloxycarbonylketimines from *N*-trimethylsilylimines.

Recently, *N*-trimethylsilyl ketimines **4** have been directly employed in the enantioselective catalyzed reaction with allylboron reagents but their use still remains rather underdeveloped.[11] A recently devised procedure exploits a palladium-catalyzed carbonylation of *N*-unsubstituted diarylketimines **6** using aryl bromides in the presence of phosphinite ligand **7** (Scheme 2).[12] This is a rather versatile procedure that when applied to arylalkylketimines affords the corresponding enamides by virtue of a fast tautomerization of the initially formed *N*-acylketimines.

The reduced stability of unsubstituted ketimines **6** especially when alkyl ketones are required as substrates, has spurred the search for alternative substrates than ketone derivatives for the preparation of *N*-acylketimines. Azides **9** are converted into *N*-unsubstituted imines **6** by bridged diruthenium complex **11** and then acylated using mixed anhydrides **10** in a single synthetic operation (Scheme 3).[13] The catalyst



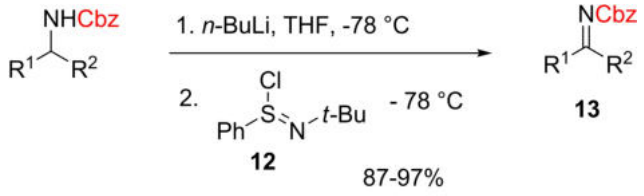
Scheme 2. Palladium-catalyzed carbonylation of *N*-unsubstituted diarylketimines.



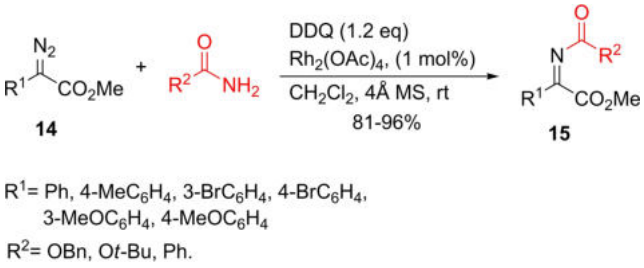
Scheme 3. Photoinduced conversion of azides into *N*-acylketimines in the presence of diruthenium complex **11**.

activity is photochemically assisted by a 30 W fluorescent lamp and quite remarkably no tautomerization to enamides or enecarbamates is observed when arylalkyl azides or dialkyl azides are employed as substrates. The process shows an outstanding versatility being applicable even to cyclic azides and a large variety of functionalized substrates.

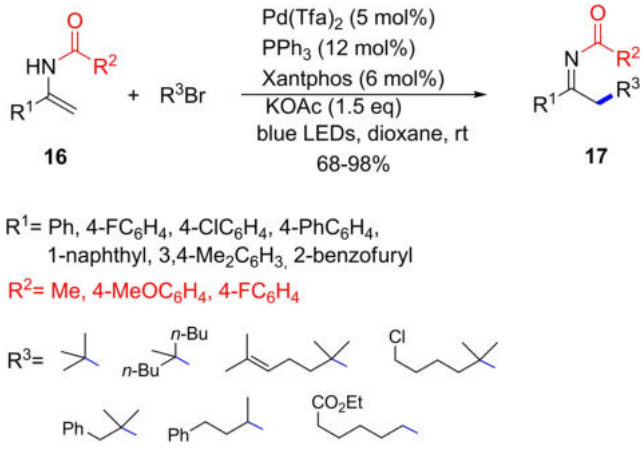
A different synthetic approach to *N*-acylketimines has been envisaged in the oxidation of *N*-benzyloxycarbonylamines using *N*-*t*-butylbenzene-sulfinimidoyl chloride **12** at very low temperature (Scheme 4).[14] The oxidation is effective on the deprotonated carbamate and generally affords good yields of the target ketimines **13** although in some examples substantial amounts of the tautomeric enecarbamates are also formed. The procedure envisaged for the preparation of α-ketimino esters **15** merges two distinct reactions, namely the rhodium-catalyzed conversion of α-diazo esters **14** into *N*-acylamino esters and their oxidation to the corresponding ketimine by DDQ (Scheme 5).[15] This tandem process is particularly effective for the preparation of Cbz and Boc imino derivatives but is also usable for the synthesis of *N*-diphenylphosphinoylketimino esters although this possibility has been exploited only for a single example.



Scheme 4. Oxidation of *N*-benzyloxycarbonylamines.



Scheme 5. Tandem amidation-oxidation of α-diazo esters.



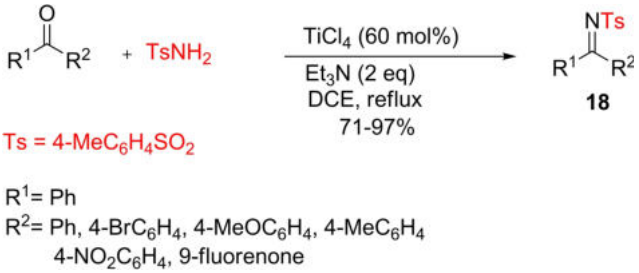
Scheme 6. Palladium-catalyzed alkylation of enamides.

Finally, the palladium-catalyzed alkylation of enamides **16** using alkyl bromides provides in a very efficient way *N*-acylketimines **17** (Scheme 6).[16] The reaction is activated by blue LEDs irradiation and is effective for a wide array of functionalized primary, secondary and tertiary alkylating agents. The mechanism supposedly involves the formation of a photochemically produced hybrid alkyl Pd(I)-radical species which regioselectively adds to the enamide substrate.

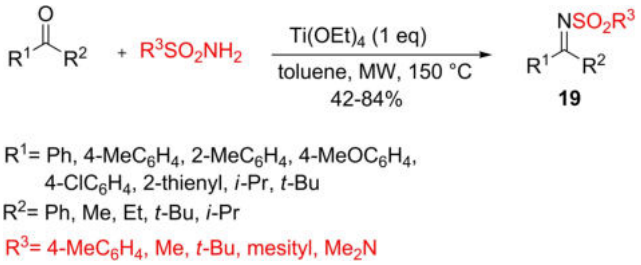
2.2. *N*-Sulfonylketimines

Unlike *N*-acylketimines, the sulfonyl analogues can be obtained by direct condensation of ketones with arylsulfonylamides in the presence of Lewis acids. The reaction conditions can be appropriately adapted according to the nature of the ketone used as substrate. Diaryl ketones can be converted into the corresponding *N*-tosylketimines **18** using tosylamide in the presence of titanium(IV) chloride (Scheme 7).[17]

This procedure is poorly effective using enolizable ketones which require a modified version of this protocol. Titanium(IV) ethoxide is employed as activator without any added base but microwave irradiation at high temperature in toluene (Scheme 8).[18] Obviously, this procedure is also effective on diaryl ketones providing better results over the previously described method. Alternative methods for the preparation of *N*-sulfonylketimines entail the oxidation of *N*-sulfinylketimines using *m*-chloroperoxybenzoic acid,[19] the oxidation of *N*-sulfonamides using diacetoxyiodoben-



Scheme 7. Direct condensation of tosylamide with diaryl ketones.



Scheme 8. Direct condensation of tosylamide with enolizable ketones.

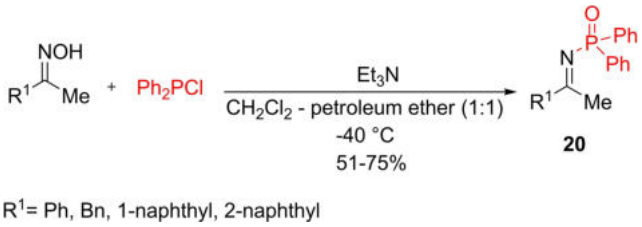
zene mediated by *N*-hydroxyphthalimide,[20] or the oxidation of *N*-tosyl α-aminophosphonates by *N*-chlorination/elimination.[21] Considering the viability of the direct condensation procedures these latter methods have been seldom used for synthetic purposes.

2.3. *N*-Phosphinoylketimines

The leading protocol for the preparation of *N*-phosphinoylketimines has been introduced several years ago but is still the most effective for a wide array of ketone derivatives. Ketones are converted into oximes which upon treatment with chlorodiphenylphosphine afford the corresponding *N*-diphenylphosphinoylketimines **20** (Scheme 9).[22]

The proposed mechanism entails the formation of a phosphorus (III) oxime ester which upon rearrangement involving radical intermediates finally affords the ketimine **20**. This procedure shows a very large substrate applicability and can also be used for the preparation of *N*-phosphinoyl azadienes from enone oximes.[23] A direct method similar to that employed for the preparation of *N*-sulfonylimines **19** reacting ketones with diphenylphosphinamide in the presence of titanium(IV) ethoxide has been occasionally employed for a limited number of substrates.[24] This procedure when applied to particularly reactive trifluoromethylaryl ketones leads to the formation of hemiaminals **21** which are stable precursors of the corresponding *N*-diphenylphosphinoylketimines (Scheme 10).[25]

Recently, a versatile method for the preparation of functionalized *N*-phosphinoylketimines **22** by reaction of *N*-unsubstituted imines **6** with diarylphosphine oxides has been proposed (Scheme 11).[26] The procedure is based on the oxidation of the iodide anion to hypoiodous acid which subsequently converts diarylphosphine oxides into phosphoryl iodides. The latter intermediates react with imines **6** leading to compounds **22** through a nucleophilic substitution.

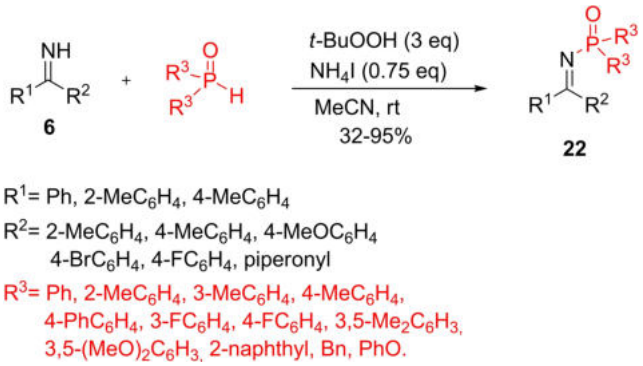


Scheme 9. Phosphinoylation of oximes with chlorodiphenylphosphine.

Scheme 10. Synthesis of *N,O*-acetals by condensation of diphenylphosphynoyl amide with trifluoromethyl ketones.

3. Reaction with Organometallic and Organoboron Reagents

The addition of organometallic reagents to imino derivatives is often limited by the strongly basic character of the nucleophile which favors the enolization rather than the nucleophilic addition. For this reason, the initial studies on the enantioselective catalyzed additions to ketimines have been carried out using non-enolizable substrates and organometallic reagents endowed of a reduced basicity. As previously reported in Scheme 10, hemiaminals **21** can be obtained as stable compounds which under basic conditions are converted into the corresponding ketimines. Thus, compounds **21** can be used as substrates in the copper-catalyzed reaction with simple alkylzinc reagents which also provide the basic environment to convert hemiaminal **21** into the reactive ketimine **21 a**

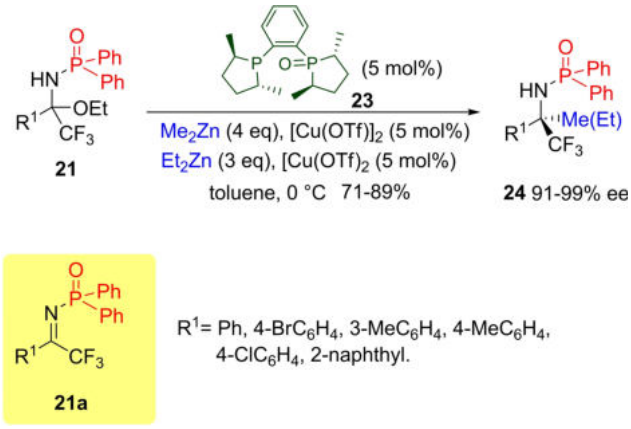


Scheme 11. Oxidative phosphonylation of *N*-unsubstituted imines with diarylphosphine oxides.

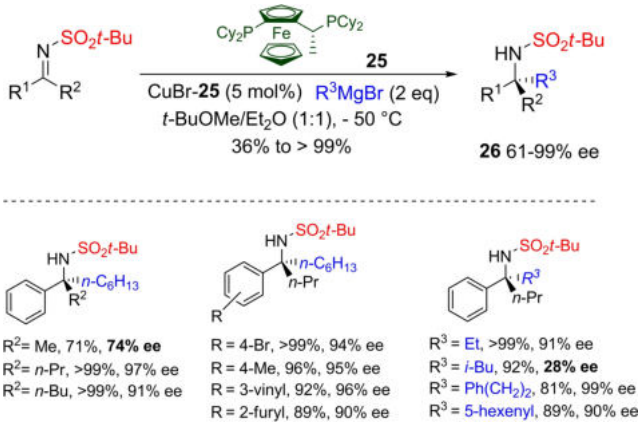
(Scheme 12).[25] The reaction occurs in the presence of the chiral BozPHOS ligand **23** and although limited to simple dialkylzinc reagents affords the corresponding amino derivatives **24** in good yields and enantioselectivities. The enantioselective conjugate addition of dimethylzinc to α,β-unsaturated *N*-(2-pyridyl)sulfonyl ketimines has been carried out using a copper-phosphoramidite complex.[27] The corresponding *N*-arylsulfonyl enamines are obtained in good yields and high *Z* selectivity but moderate enantioselectivity (71–80%). Organolithium reagents can be involved in asymmetric processes using ketimines only in the presence of superstoichiometric amount of chiral ligands.[28] Conversely, various Grignard reagents can be efficiently added to enolizable ketimines in the presence of a copper complex with chiral diphosphine **25** at low temperature (Scheme 13).[29] Among various activated ketimines *N*-*t*-butylsulfonylketimines gave the best results in terms of enantioselectivity. The yields and ees of this process are usually remarkably high except when hindered Grignard reagents and simple methylphenyl *N*-*t*-butylsulfonylketimine are used.

Organometallic catalysts generally act through a fast scrambling of one or more ligands with the reactants in order to ensure an efficient catalytic cycle. This issue is particularly crucial in asymmetric processes in order to obtain high levels of enantioselectivity. In the alkynylation of trifluoromethylketimino esters, the (phebox)rhodium complex **27** embedding a trimethylsilylalkynyl group has been revealed far superior to any other related catalyst in which only acetoxy groups are contained as removable ligands (Scheme 14).[30] The outstanding performance of complex **27** allows a notable reduction in the catalyst charge (0.5 or 2.5 mol%) over related catalysts depending on the nature of the R^1 group in the alkyne and enables the formation of amino acid derivatives **28** in high yields and enantioselectivity. The new catalytic species **I** formed by alkyne exchange from **27** reacts with the ketimine leading to intermediate **II** which upon reaction with the alkyne reagent affords the target product **28** regenerating the active catalyst **I**.

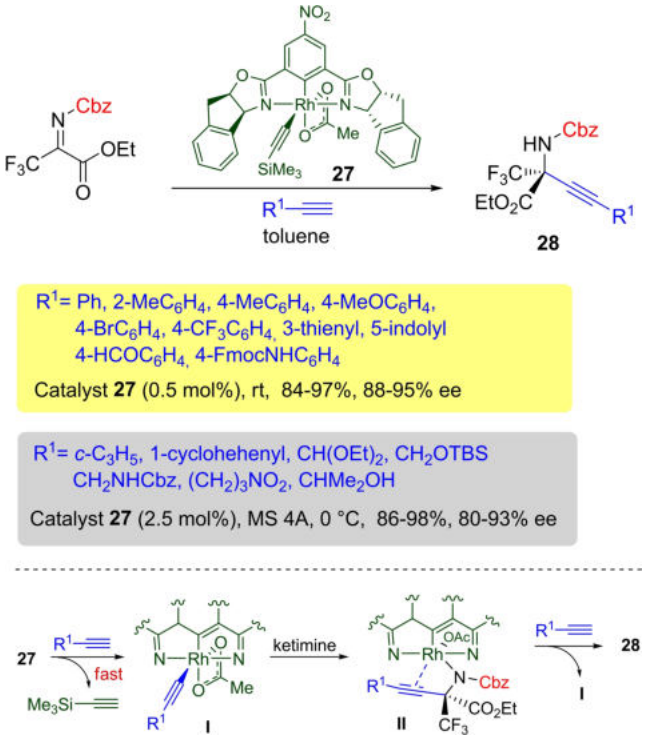
The same procedure is also effective on trifluoromethylketimino phosphonates although a higher charge of catalyst **29** is required for the preparation of alkynylamido phosphonates **30** (Scheme 15). Rhodium complexes with chiral diene ligands are effective in the reaction of *N*-arylsulfonylketimines with aryl



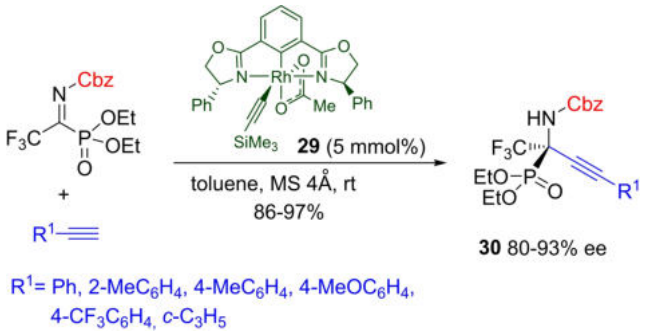
Scheme 12. Dialkylzinc additions to *N,O*-acetals in the presence of BozPHOS ligand **23**.



Scheme 13. Enantioselective addition of Grignard reagents to sulfonylketimines catalyzed by copper-diphosphine complex.



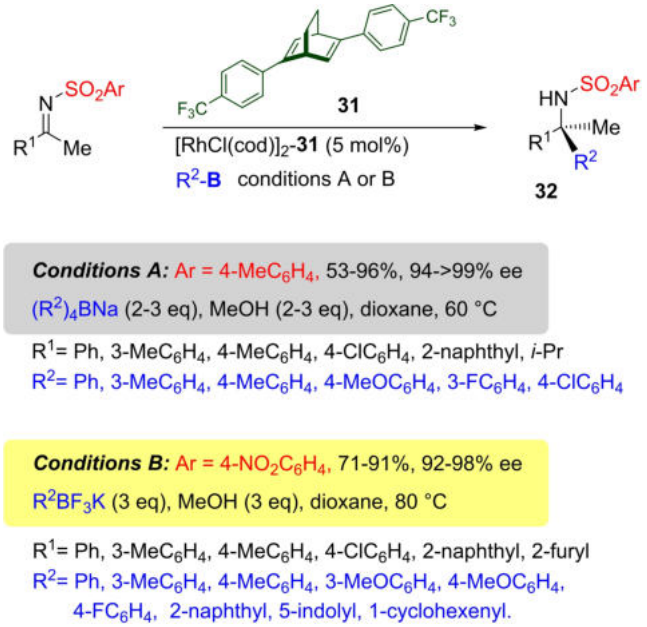
Scheme 14. Alkynylation of trifluoromethylketimino esters using rhodium complex **27**.



Scheme 15. Alkynylation of trifluoromethylketimino phosphonates using rhodium complex **29**.

and alkenylboron reagents. The first enantioselective catalyzed arylation of *N*-tosylketimines has been carried out using sodium tetraarylborates in the presence of a rhodium complex with chiral ligand **31** (Scheme 16, conditions A).[31] This process is quite efficient in term of chemical yield and enantioselectivity but is poorly atom economic since only one aryl group is transferred to the target product. Later on this procedure has been somewhat improved moving to potassium aryltrifluoroborates which allow the addition of various aryl and alkenyl frameworks in *N*-nosylketimine substrates (Scheme 16, conditions B).[32]

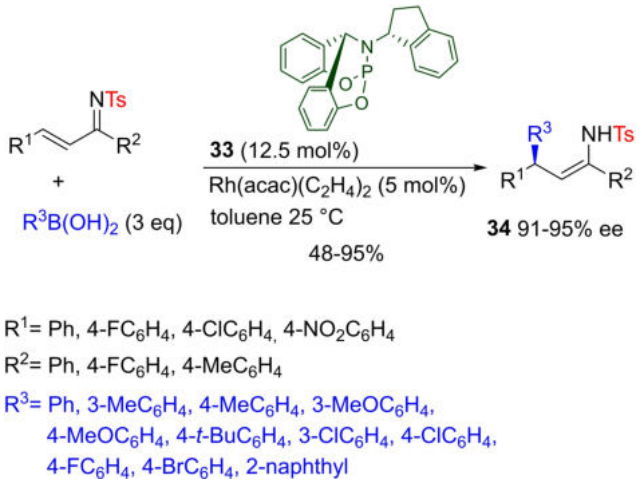
Arylboronic acids in the presence of the rhodium complex with chiral bicyclic bridgehead phosphoramidite ligands **33** are effective reagents for the 1,4-arylation of α,β-unsaturated *N*-tosylketimines



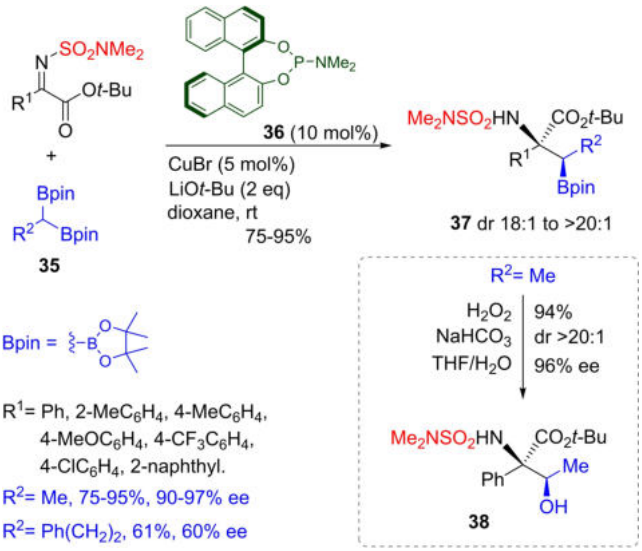
Scheme 16. Reaction of arylboron reagents with arylsulfonylketimines catalyzed by rhodium-diene **31** complex.

(Scheme 17).[33] The corresponding *N*-tosylenamines **34** are obtained in high yield and excellent enantioselectivity.

The diastereo- and enantioselective reaction of 1,1-diborylpinacolatoalkanes **35** with *N*-sulfamoyl-ketimino esters catalyzed by copper(I) bromide in the presence of chiral ligand **36** affords the corresponding adducts **37** in generally good yield (Scheme 18).[34] The reaction conditions have been optimized for cyclic ketimino derivatives but have also been proved effective for open-chain ketimino esters, although the best results can be obtained using the simple methyl derivative (**35**, R^2 = Me). The particular synthetic interest in derivatives **37** stems on the possibility of



Scheme 17. Conjugate addition of arylboronic acids to α,β-unsaturated *N*-tosylketimines catalyzed by rhodium- bridgehead phosphoramidite **33** complex.



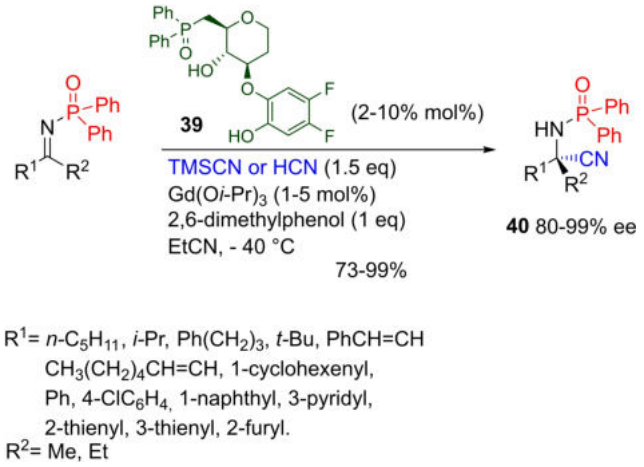
Scheme 18. Reaction of diboryl derivatives **35** with ketimino esters catalyzed by copper-ligand **36** complex.

stereospecifically convert the boryl group into a hydroxy group as demonstrated for the single preparation of 2-amino-3-hydroxy ester derivative **38** fully retaining the configuration of the originally formed stereocenters.

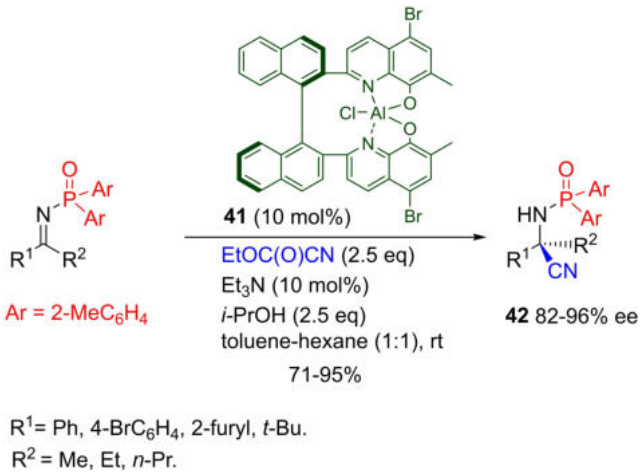
4. The Strecker Reaction

The Streker amino acids synthesis involves the addition of cyanide anions to preformed or *in situ* generated imino derivatives followed by the hydrolysis of the resulting aminonitrile. The interest in the preparation of optically active unnatural amino acids has spurred the search for increasingly efficient protocols for the Strecker synthesis.[35] These often include the substitution of highly toxic alkali cyanide salts with alternative cyanide delivering reagents endowed of superior safety features. Pioneering studies of the enantioselective Strecker reaction on activated ketimines have been conducted on *N*-phosphinoylketimines using a chiral lanthanide complex obtained mixing gadolinium(III) isopropoxide and D-glucose derived ligand **39** (Scheme 19).[36] The actual catalyst is composed by a 2:3 ratio of the metal/ligand species,[37] and the activity of the complex is based on the preliminary cyanation of a single metal atom followed by a Lewis acid-base interaction of the other metal atom with the phosphinoyl oxygen of the ketimine. Intramolecular release of the cyanide anion to the ketimine completes the process leading to adducts **40**. The synthetic protocol has been improved by addition of a stoichiometric amount of 2,6-dimethylphenol as reported in Scheme 19.[38]

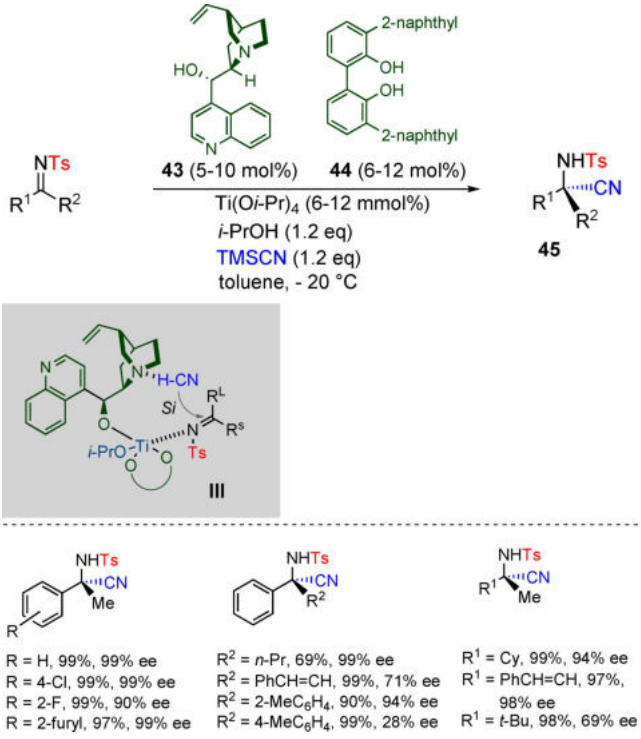
The chiral aluminum complex **41** is also effective in the reaction of *N*-diarylphosphinoylketimines with ethyl cyanoformate (Scheme 20).[39] Activation of the cyanide ion donor is ensured by a catalytic amount of triethylamine, while isopropanol improves the catalyst turnover assisting the cleavage of the aluminum-amide bond formed between the catalyst and the generated product **42**. Cinchona alkaloids are used as organocatalysts in many synthetic processes but can also be involved in metal-catalyzed reactions. A mixture of cinchonine **43**, biphenol **44** and titanium (IV) isopropoxide works as a very efficient catalyst in the reaction of *N*-tosylketimines with trimethylsilyl cyanide (Scheme 21).[40]



Scheme 19. Cyanation of *N*-diphenylphospinoylketimines catalyzed by gadolinium-ligand **39** complex.



Scheme 20. Reaction of *N*-diarylphospinoylketimines with ethyl cyanoformate catalyzed by aluminum complex **41**.



Scheme 21. Titanium-catalyzed cyanation of *N*-tosylketimines in the presence of chinchonine **43** and biphenol **44**.

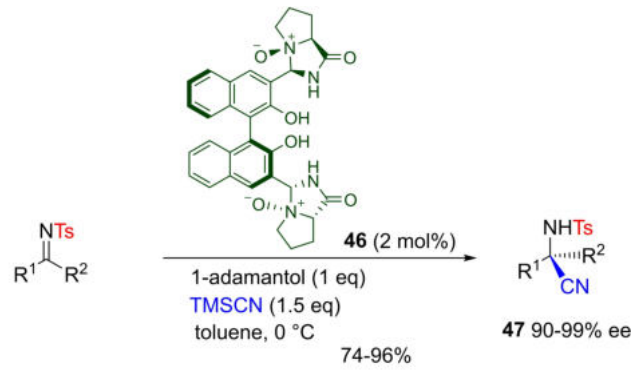
The interaction of these three components probably generates a new titanium alkoxide species which is able to interact with the ketimine by a Lewis acid-base interaction and hydrogen cyanide formed by reaction of trimethylsilyl cyanide and isopropanol. According to the plausible transition state **III**, the cyanide ion attacks the *Si* face of the ketimine leading to the preferential formation of the *S* enantiomer of the target products **45**. The best enantioselectivity levels are obtained using groups of very different size on the substrate. Diarylketimines bearing *ortho* substituents affords products **45** with excellent enantioselectivity while the steric features of *para*-substituted substrates do not allow a pronounced differentiation between the aryl groups. Other metal-chiral ligands combinations have been exploited for this reaction but the efficiency is not comparable with that observed in the previous examples.[41] A very efficient organocatalyzed method for the enantioselective Strecker reaction on *N*-tosylketimines has been devised using binapthol-based *N*-oxide catalyst **46** (Scheme 22).[42] Previous studies carried out using a simplified version of catalyst **46** led to exclude the formation of hydrogen cyanide as active species generated from trimethylsilyl cyanide.[43] A plausible mechanism would involve the activation of trimethylsilyl cyanide by the two *N*-oxides forming an hypervalent silicate. Besides, the ketimine activation is achieved by hydrogen bonding brought by the naphthol units and the lactam NH bonds.

A related procedure has been devised using *N*-phosphinoylketimines, generating the *N*-oxide catalyst *in situ* by oxidation of the corresponding tertiary amines.[44] Although satisfactory, the obtained results are less striking than those evidenced with catalyst **46**. Satisfactory levels of enantioselectivity can be obtained using commercially available catalysts such as the chiral sodium phosphate **48** in the reaction of trimethylsilyl cyanide with *N*-diphenylphosphinoylketimines (Scheme 23).[45] Formation of an hypervalent silicate is also envisaged for the present procedure involving the phosphate anion and the phenolic oxygen of the co-catalyst. The hydrogen bonding network ensures the enantiofacial discrimination in the attack of the cyanide ion to the ketimine substrate. Similarly, cinchonidine has been used without any added co-catalyst in the cyanation of α-ketimino phosphonates.[21] Acetyl cyanide in chloroform at room temperature has been revealed far superior than any other cyanide reagents leading to the corresponding Strecker products in satisfactory yields and enantioselectivity (73–92% ee).

The Strecker reaction on *N*-*t*-butoxycarbonyl-trifluoromethylarylketimines has been recently achieved using trimethylsilyl cyanide and a dual catalytic system made by chiral phosphine-thiourea **50** and methyl acrylate (Scheme 24).[46] The catalytic action is supposed to start by a conjugate addition of the phosphine moiety to methyl acrylate that generates an enolate anion which activates trimethysilyl cyanide toward the nucleophilic addition. According to transition state **IV**, the ketimine, activated by hydrogen bonding with the thiourea, undergoes a selective attack to the *Si* face of the molecule leading to enantioselective formation of products (*S*)-**51**. It is interesting to remark that this process is equally effective on *N*-*p*-methoxyphenylketimines which because of a different arrangement in the transition state afford aminonitriles with *R* configuration.

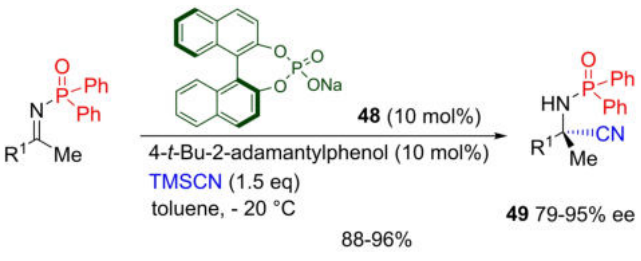
5. The Nitro-Mannich Reaction

The aza version of the Henry nitroaldol reaction, often referred as the nitro-Mannich reaction, is one of the leading processes enabling the synthesis of β-amino



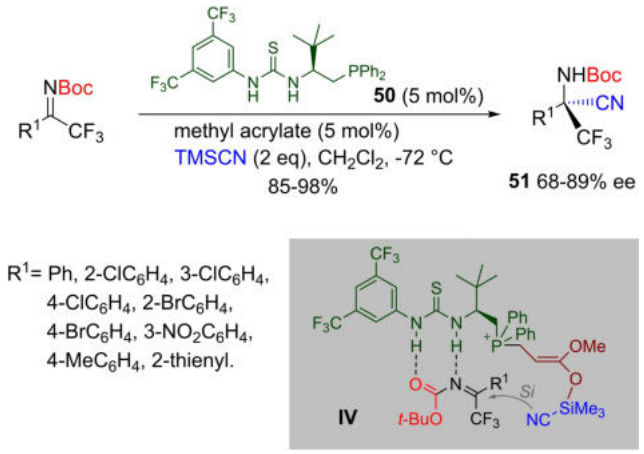
R^1= Ph, 2-FC_6H_4, 4-FC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 2-MeC_6H_4, 4-MeC_6H_4, 2-$MeOC_6H_4$, 4-$MeOC_6H_4$, 3,4-$(MeO)_2C_6H_3$, 2-naphthyl, 2-furyl, 2-thienyl, PhCH=CH, *t*-Bu.
R^2= Me, Et, *n*-Pr, Ph

Scheme 22. Organocatalyzed cyanation of *N*-tosyl-ketimines by chiral *N*-oxide **46**.



R^1= Ph, 4-BrC_6H_4, 4-FC_6H_4, 2-ClC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 3-$NO_2C_6H_4$, 4-$NO_2C_6H_4$, 3-MeC_6H_4, 4-MeC_6H_4, 3$MeOC_6H_4$, 4-$MeOC_6H_4$, 2-naphthyl, 2-furyl, Cy, *t*-Bu.

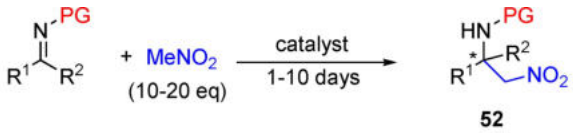
Scheme 23. Organocatalyzed cyanation of *N*-diphenyl- phosphinoylketimines by chiral sodium phosphate **48**.

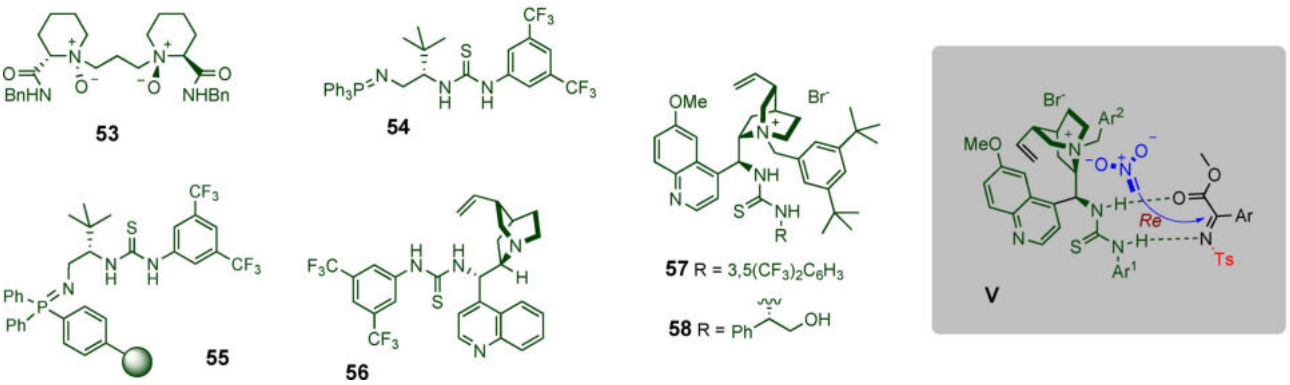


Scheme 24. Organocatalyzed cyanation of *N*-t-butoxycarbonyl-ketimines by chiral thiourea **50**.

functionalized compounds.[47] As a matter of fact, the nitro group in the resulting 2-nitroamines can be reduced to 1,2-diamines or converted into 2-amino-carbonyl systems using the Nef reaction.[48] The asymmetric nitro-Mannich reaction has been carried out mainly on aldimine derivatives using nitromethane as well as primary nitrocompounds. The reduced reactivity of ketimines, even when appropriately activated, practically limits the nitro-Mannich reaction to the exclusive use of nitromethane. The first enantioselective addition of nitromethane to *N*-arylsulfonylketimines was catalyzed by a chiral copper complex with *N*-oxide **53** derived from (S)-pipecolic acid (Table 1, entry 1).[49] The efficiency of the process is strongly affected by the reaction time which must be around ten days. Later on, different thiourea based catalysts have been devised for this reaction starting from chiral bifunctional iminophosphorane **54** (Table 1, entry 2).[50] The good performances shown by catalyst **54** were maintained using the polystyrene-bound version **55** which allows easy recoverability and reusability for more than ten runs (Table 1, entry 3).[51] The reaction of nitromethane with *N*-arylsulfonylketiminophosphonates has been realized using bifunctional thiourea catalyst **56** (Table 1, entry 4).[52] The obtained α-amino-β-nitrophosphonates can be reduced under mild reaction conditions to the corresponding chiral

Table 1. Enantioselective nitro-Mannich reaction of nitromethane with *N*-activated ketimines.





Entry	PG	R^1	R^2	Catalyst (mol%)	Conditions[a]	Yield (%)	Ee (%) [abs.conf.]	Ref.
1	*p*-$TolSO_2$	Aryl, Cy	Me, Et	**53** (20)[b]	PhOEt, 4 Å MS, 0 °C	30–83	71–96 [*S*]	[49]
2	$Ph_2P{=}O$	Aryl, Cy	Me, Et	**54** (10)	Neat, −15 or 0 °C	62–97	18–95 [*S*]	[50]
3	$Ph_2P{=}O$	Aryl	Me, Et	**55** (10)	PhMe, 0 °C	71–96	86–94 [*S*]	[51]
4	*p*-$TolSO_2$	Aryl	$(i\text{-PrO})_2P{=}O$	**56** (10)	PhMe, rt	82–87	80–84 [*S*]	[52]
5	*p*-$TolSO_2$	Aryl	CO_2Me(Et)	**57** (10)[c,d]	*m*-Xylene, −10 °C	78–99	67–99 [*R*]	[53]
6	Boc	Aryl	CF_3	**58** (5)[c]	Toluene, −20 °C	90–98	92–96 [*R*]	[54]

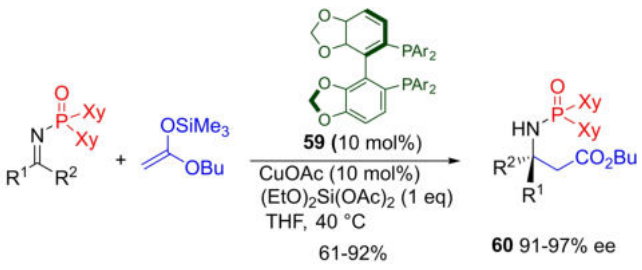
[a] Excess of nitromethane (10-20 eq) was used.
[b] $(CuOTf)_2{\cdot}C_7H_8$ (10 mol%) was added.
[c] $LiOH{\cdot}H_2O$ (5 eq) was added.
[d] Reaction time 3 h.

diamino acid derivatives. Similarly, *N*-arylsulfonylketimino esters react with nitromethane in the presence of bifunctional quaternary ammonium salt **57** (Table 1, entry 5).[53] The superior electrophilic reactivity of these ketimino esters allows a notable shortening of the reaction time to 3 hours over several days experienced with the corresponding arylalkyl analogues. Finally, outstanding results have been obtained in the reaction of nitromethane with trifluoromethylated ketimines using quaternary ammonium salt **58** (Table 1, entry 6).[54] The activation of nitromethane by thiourea-based catalysts is usually due to the strong hydrogen bonding occurring between the nitro oxygen atoms of the nitronate anion and the acidic NH of the thiourea. However, with ammonium salt catalysts **57** and **58** the electrostatic interactions between the nitronate and the ammonium moiety appear to play a major role in the transition state **V**. Thus in this instance, activation of the electrophile seems brought by the Brønsted interactions of the acidic NH bonds with the basic centers of the ketimine.

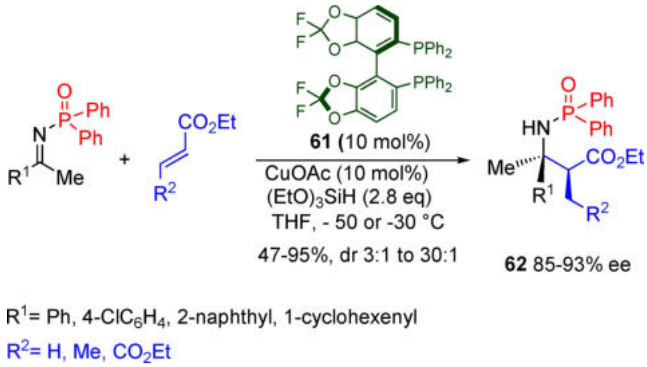
6. The Mannich Reaction

The addition of carbonyl and ester enolates to azomethine systems is generally indicated as the Mannich reaction. Along the years, this named reaction has been extended to every addition of stabilized carbanions to imino derivatives. The first enantioselective reaction on activated arylalkyl ketimines has been carried out using a silyl ketene acetal in the presence of a copper-diphosphine **59** complex (Scheme 25).[55] This approach allows an efficient entry to optically active β-amino acid derivatives **60** bearing a quaternary stereocenter. The mechanism probably involves the intermediate formation of a copper enolate and the appropriate catalyst turnover is favored by the silicate additive which breaks the intermediate copper amide formed after the nucleophilic addition. Attempt to use long chain silyl ketene acetals or ester enolates was ineffective under these conditions. However, a reductive Mannich reaction of *N*-diphenylphosphinoylketimines with α,β-unsaturated esters has been proposed by the same research group in the presence of (*R*)-difluorophos ligand **61** using triethoxysilane as reducing agent (Scheme 26).[56] A copper enolate is supposed to be the reactive species also in this procedure which affords the corresponding adducts **62** with satisfactory diastereo- and enantioselectivity.

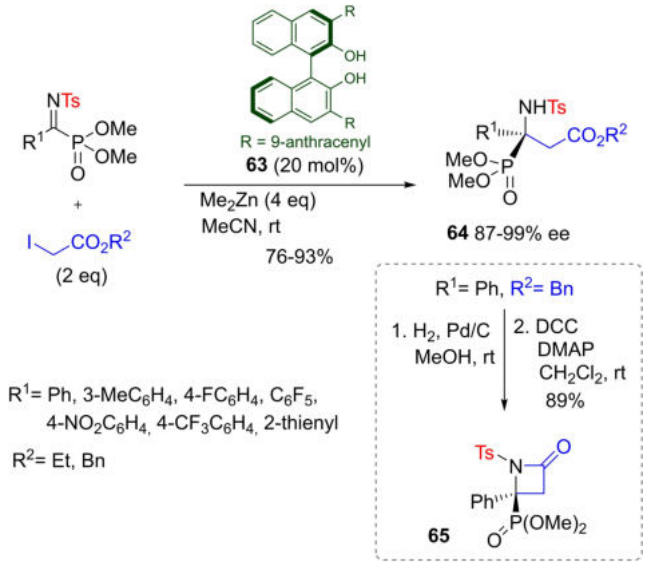
Simple non-activated esters have been employed only recently exploiting the aza-Reformatski reaction of α-phosphinoyl-*N*-arylsulfonylketimines with zinc enolates generated from iodoacetates and dimethylzinc (Scheme 27).[57] The addition is catalyzed by binaphthol derivative **63** and affords phosphorated analogues



Scheme 25. Reaction of a silyl ketene acetal to *N*-diarylphosphinoylketimines catalyzed by copper-diphosphine **59** complex.



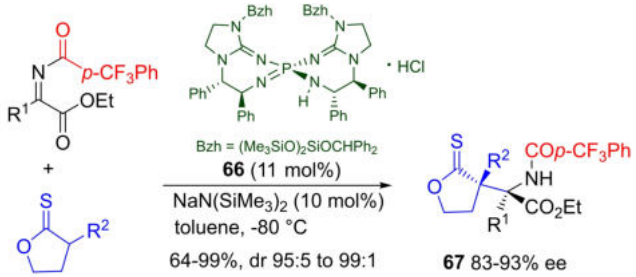
Scheme 26. Reductive Mannich reaction of α,β-unsaturated esters catalyzed by copper-diphosphine **61** complex.



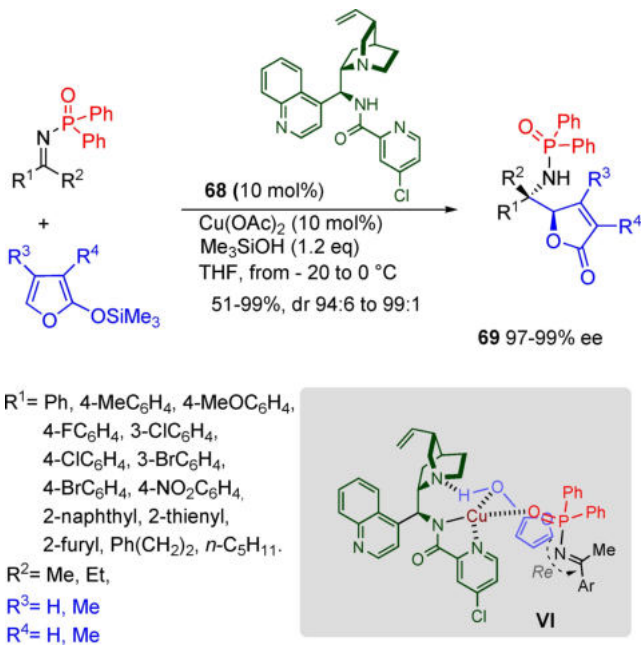
Scheme 27. Enantioselective addition of zinc ester enolates to α-phosphinoyl-*N*-arylsulfonylketimines.

of aspartic acid **64** in good yield and enantioselectivity. The usefulness of the obtained products has been demonstrated converting one of them in the β-lactam derivative **65.**

Chiral superbases such as bis(guanidino)-iminophosphorane **66** have been successfully employed in the addition of α-substituted thionolactones to *N*-acylketimino esters (Scheme 28).[58] The superbase hydrochloride is activated by a catalytic amount of sodium hexamethyldisilazide and is effective for the synthesis of densely functionalized adducts **67** in high diastereo- and enantioselectivity. It is interesting to



Scheme 28. Addition of α-substituted thionolactone enolates to *N*-acylketimino esters catalyzed by chiral superbase **66**.

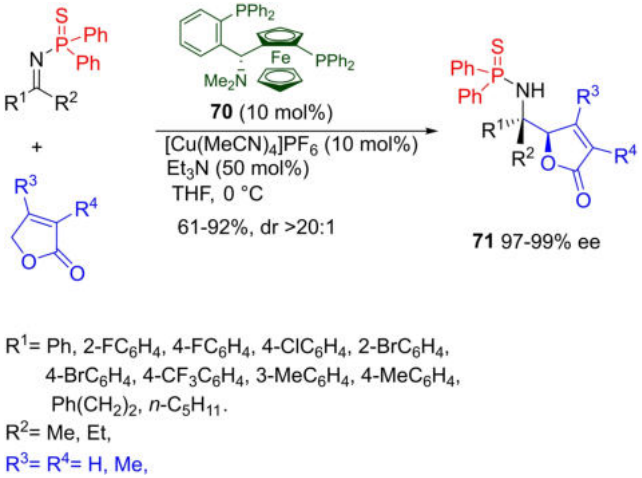


Scheme 29. Reaction of trimethylsilyloxyfuran with *N*-diphenylphosphinoylketimines catalyzed by copper-ligand **68** complex.

observe that α-substituted lactones are unreactive under the same reaction conditions. This is probably due to the superior acidity of the α hydrogens in thionolactones compared to their oxygenated analogues. 2-Trimethylsilyloxyfuran can be considered as a cyclic dienol synthon amenable to be used in vinylogous Mannich reactions with imino derivatives.

Reaction of *N*-diphenylphosphinoylketimines with 2-trimethylsilyloxyfuran in the presence of organocatalyst **68** and copper(II) acetate affords the *anti* adducts **69** with an excellent level of diastereo- and enantioselectivity (Scheme 29).[59] The copper complex formed by interaction of **68** with the metal salt is able to coordinate the reactants allowing a stereoselective addition of the dienol system to the *Re* face of the ketimine according to transition state **VI**. Monomethyl 3 or 4 substituted 2-trimethylsilyloxy- furans can also be successfully employed in this reaction while the presence of substituents at 5 position of the furan reagent does not give rise to any product **69**.

The direct utilization of γ-butenolides in the same process has also been devised using *N*-diphenylthiophosphonylketimines in the presence of the copper complex with chiral taniaphos **70** (Scheme 30).[60] A reactive dienolate anion can be readily obtained by deprotonation of the γ-butenolide with triethylamine while the presence of the sulfur atom in the ketimine ensures an appropriate interaction with the metal of the chiral complex. Compounds **71** obtained can be converted into lactam derivatives after a simple double bond reduction of the butenolide unsaturation and reductive cleavage of the thiophosphinoyl group. Dechlorinated catalyst **68** has been proved effective in the reaction of γ-butenolides with *N*-phosphinoyl ketimines in the presence of zinc(II) triflate.[61] Selective formation of the *anti* stereoisomer of products **69** is observed although the enantioselectivity

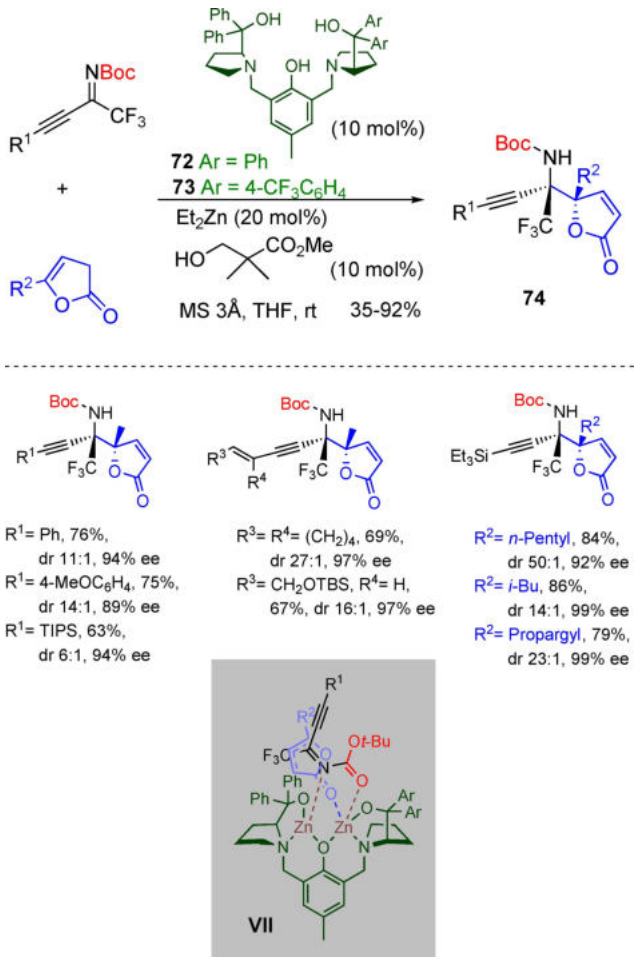


Scheme 30. Addition of γ-butenolides to *N*-thionophosphonylketimines catalyzed by chiral copper-diphosphine **70** complex.

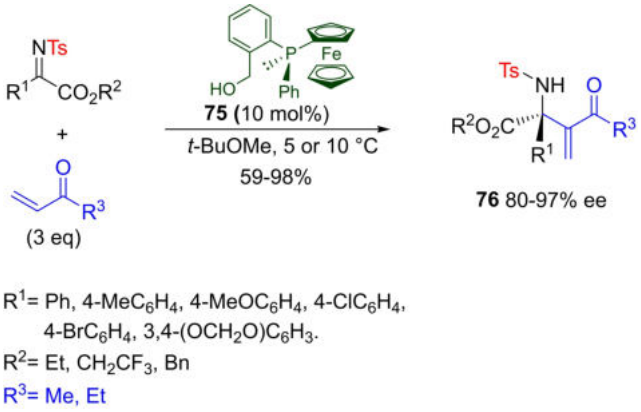
recorded with this method is lower compared to those previously released (80–88% ee). The reaction of *N*-*t*-butoxycarbonylalkynyl-trifluoromethylketimines with unconjugated γ-butenolides can be carried out using the chiral zinc complex with bisprolinolphenol ligands **72** and **73** (Scheme 31).[62]

The resulting highly functionalized products **74** are formed with excellent diastereo- and enantioselectivity allowing further synthetic manipulations at both the alkynyl moiety and butenolide portion. The nucleophilic attack of the unconjugated butenolide occurs regioselectively at the γ position although a minor amount of the α-regioisomer is always formed (rr 4:1 to 50:1). A rationale for the observed stereoselectivity of this reaction entails the interaction of the ketimine and the butenolide Lewis basic atoms with the coordinating zinc of the complex as suggested by the transition state model **VII**. The aza-Morita–Baylis–Hillman reaction (aza-MBH) of enones with *N*-tosylketimino esters catalyzed by chiral phosphine **75** affords the corresponding adducts **76** in good yield and enantioselectivity (Scheme 32).[63]

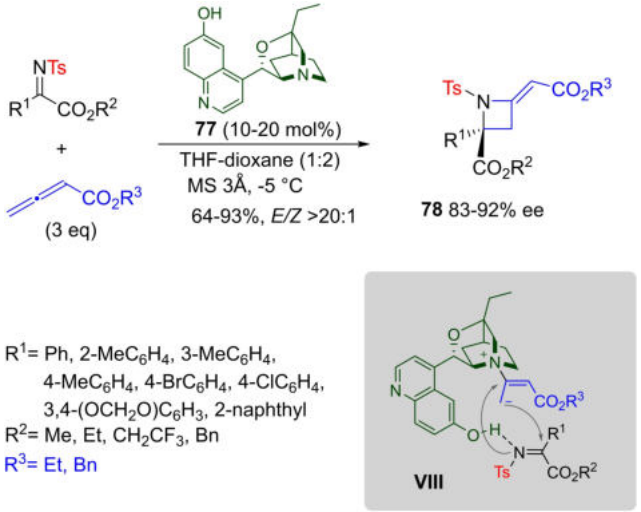
The mechanism of the aza-MBH reaction entails the preliminary formation of a bulky zwitterionic intermediate by conjugate addition of the phosphine to the enone. The resulting enolate reacts with the ketimine substrate and by subsequent elimination of the phosphine the unsaturation is restored and the catalyst regenerated. The steric hindrance of the zwitterionic intermediate prevents the reaction with ketimines bearing *ortho*-substituted aryls and *t*-butyl groups. The reaction of allenoates with *N*-tosylketimino esters in the presence of β-isocupreidine **77** affords azetidines **78** through a formal [2+2] cycloaddition (Scheme 33).[64] Products **78** are obtained with high *E* diastereoselectivity and satisfactory enantioselectivity and can be converted into azetidinones and other



Scheme 31. Reaction of unconjugated γ-butenolides with *N*-t-butoxycarbonylalkynylketimines catalyzed by zinc-bisprolinophenol complexes.



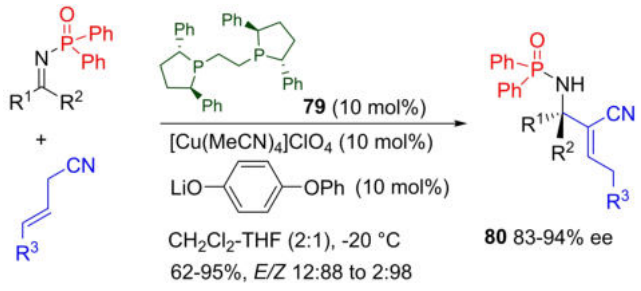
Scheme 32. Aza-MBH reaction of enones with *N*-tosylketimino esters catalyzed by chiral phosphine **75**.



Scheme 33. Enantioselective synthesis of azetidines by aza-MBH reaction of allenoates with *N*-tosylketimino esters catalyzed by β-isocupreidine.

derivatives by oxidative or reductive reactions. This process can be considered as an aza-MBH reaction in which the attack of the nitrogen atom of the catalyst to the allenoate generates a vinylogous ester enolate. The addition to the ketimines by the enolate occurs regioselectively at γ-position and is followed by a ring closure as indicated in the transition state **VIII**.

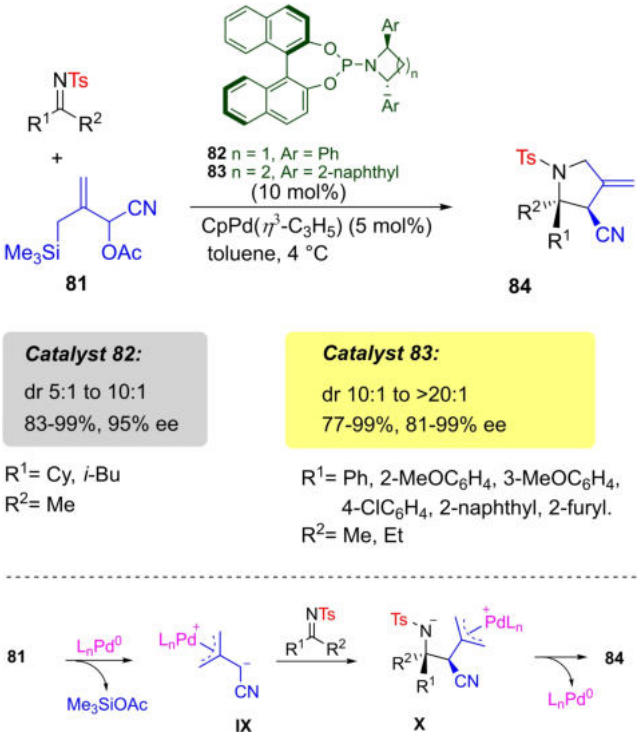
The reduced steric hindrance of the nitrile group makes the corresponding α-anions particularly reactive in addition reaction with azomethine systems. Thus, allylic cyanides react with *N*-diphenylphosphinoylketimines in the presence of the copper complex with chiral diphospholane catalyst **79** leading to α,β-unsaturated nitriles **80** (Scheme 34).[65] The stabilized allylic anion generated from nitriles by reaction with a lithium phenoxide reacts regioselectively at α position with the ketimine but a subsequent isomerization affords the more thermodynamically conjugated product **80** with significant *Z* diastereoselectivity. Extension of this approach to acetonitrile is also possible using different reaction conditions (iridium catalyst, Barton's base) but the enantioselectivity observed in the resulting adducts is far from satisfactory (22–68% ee).[66]



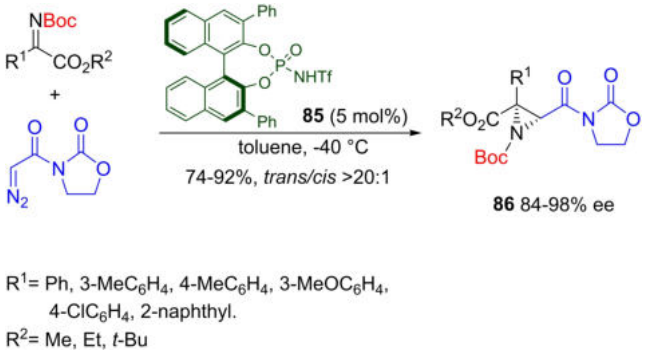
Scheme 34. Reaction of allyl cyanides with *N*-phosphinoyl ketimines catalyzed by copper-diphospholane **79** complex.

Stabilized nitrile α-anions can also be generated by palladium-catalyzed elimination of trimethylsilyl acetate from functionalized nitrile **81** (Scheme 35).[67] Reaction of **81** with *N*-tosylketimine in the presence of a palladium complex with chiral ligands **82** or **83** affords 3-cyano-4-methylene pyrrolidines **84** with high diastereo- and enantioselectivity. Ligand **82** gives the best results using dialkylketimines while ligand **83** is particularly effective with arylalkylketimines.

Formation of the target pyrrolidine compounds occurs by preliminary nucleophilic addition of the stabilized anion **IX** which upon addition with the ketimine generates the intermediate **X**. The final ring closure involving the sulfonamido anion gives the target compounds **84** and regenerates the active catalytic species. The addition of diazocarbonyl derivatives to imines is known to afford aziridines in a process involving a preliminary addition followed by ring closure entailing nitrogen gas evolution. Diazoacetyl 1,3-oxazolidinone reacts with *N*-*t*-butoxycarbonyl-ketimino esters in the presence of chiral *N*-triflylphosphoramide **85** leading to trisubstituted aziridines **86** (Scheme 36).[68] The reaction is highly *trans* diastereoselective and generally shows satisfactory levels of enantioselectivity. Active methylene compounds can generate the corresponding enolates under



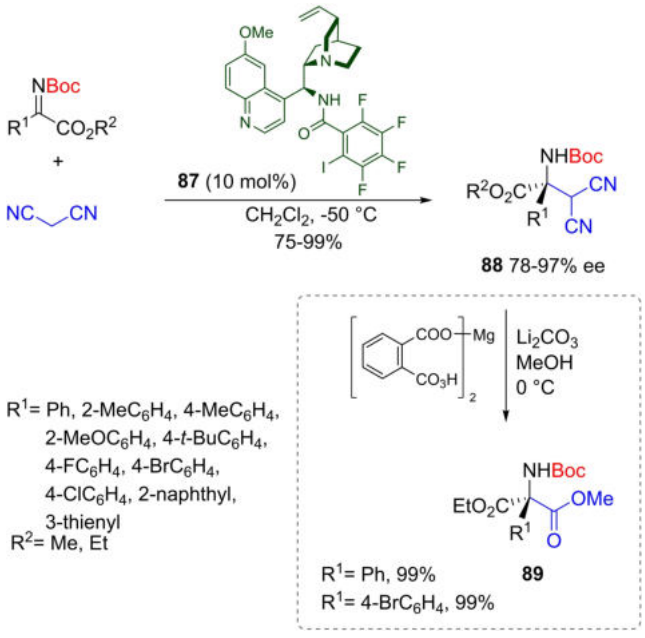
Scheme 35. Asymmetric synthesis of pyrrolidines **84** by reaction of *N*-tosylketimines with functionalized allyl cyanide **81**.



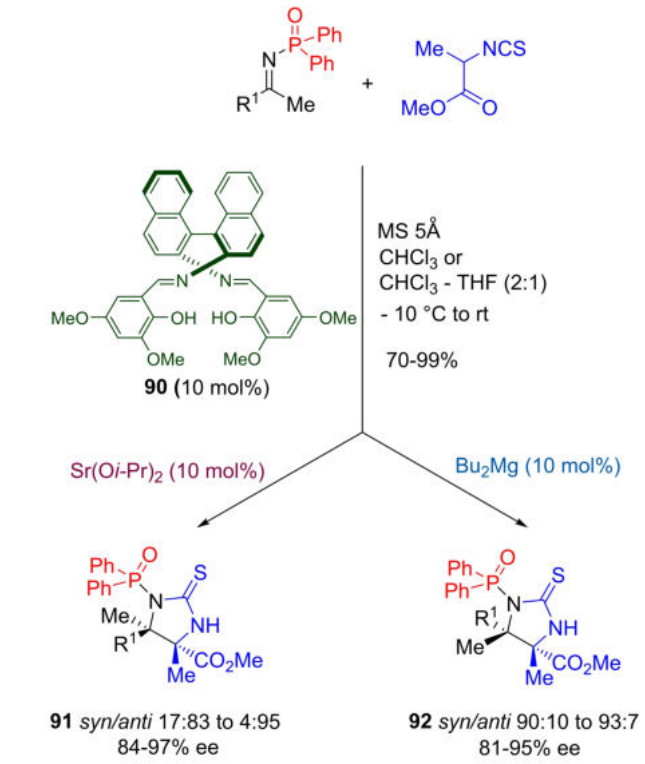
Scheme 36. Enantioselective synthesis of aziridines **86** catalyzed by palladium-phosphoramide complex.

very mild reaction conditions. Their reaction with activated ketimines has been particularly tested with those of them having a reduced steric hindrance around the nucleophilic center. Malononitrile is able to react with *N*-*t*-butoxycarbonylketimino esters at low temperature in the presence of polyhalogenated quinine-derived catalyst **87** (Scheme 37).[69] The presence of the iodine atom in the catalyst is instrumental for the enantioselectivity of the reaction since the activation of the ketimine occurs through the Lewis halogen-oxygen noncovalent interaction. As a matter of fact, the enantioselectivity of the reaction decreases moving from iodine to bromine, chlorine and fluorine atoms. The obtained products **88** show a remarkable synthetic versatility as demonstrated for their oxidative conversion into optically active aminomalonate esters **89** by reaction with magnesium monoperoxyphthalate without any erosion of the original enantiopurity.

The asymmetric addition of methyl 2-isothiocyanopropanoate to *N*-diphenylphosphinoylketimines in the presence of the chiral Schiff base **90** affords a diastereomeric couple of imidazolidine-2-thiones **91** and **92** as a result of a further intramolecular nucleophilic addition involving the isothiocyano group (Scheme 38).[70] This process occurs in a diastereodivergent fashion according to the nature of the metal ligand employed. The utilization of strontium(II) isopropoxide mainly leads to the *anti* diastereomer **91** while the *syn* diastereomer **92** predominates adding dibutylmagnesium to the reaction mixture. Circular dichroism studies evidence a different dihedral angle of the binaphthyl moiety in the two metal complexes



Scheme 37. Organocatalyzed addition of malononitrile to *N*-*t*-butoxycarbonylketimino esters.



R1= 4-BrC6H4, 4-ClC6H4, 4-FC6H4, 4-CF3C6H4, 3-MeC6H4
4-MeOC6H4, 4-Me2NC6H4, 2-thienyl, 2-furyl.

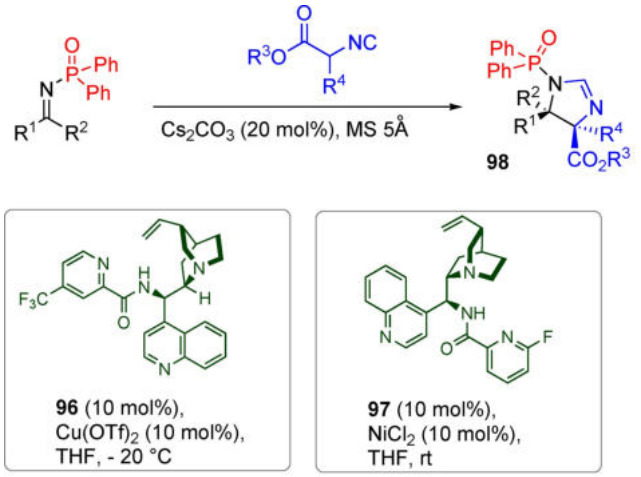
Scheme 38. Stereodivergent asymmetric synthesis of imidazolidine-2-thiones **91** and **92**.

which could be responsible for the observed opposite enantiofacial selectivity. The steric constraint around the nucleophilic center plays a fundamental role in the reactivity since the utilization of methyl 2-isothiocyanobutanoate was ineffective in this process.

Following a related strategy, 2-isocyanoacetates and their homologues can also be used in the reaction with *N*-diphenylphosphinoylketimines leading to imidazoline derivatives **95** (Scheme 39).[71] The addition is catalyzed by complexes formed by cinchona-derived aminophosphines **93** or **94** and silver(I) salts and is effective on a large variety of arylalkylketimines. Simple 2-isocyanoacetates give better performances using ligand **93** and silver(I) oxide while other alkanoate esters require the utilization of ligand **94** with silver(I) acetate. The nucleophilic attack occurs selectively to the *Re* face of the ketimine with a diastereoselectivity which is particularly high using 2-isocyanoacetate homologues. The utilization of chiral complex **94**-silver(I) oxide has been recently used for the addition of tosylmethylisocyanide (TosMIC) with *N*-diphenylphosphinoylketimines.[72] The selectivity observed in this process parallels that observed for the preparation of compounds **95**. However since the tosyl

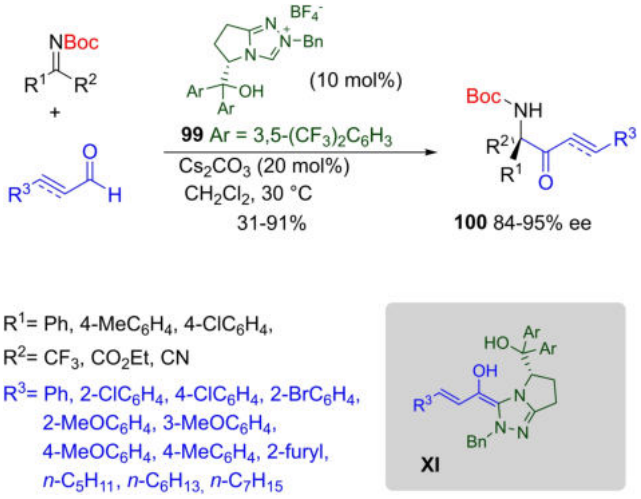
R^1	R^2	R^3	R^4	Cat.	yield (%)	dr	ee (%)
Ph	Me	$CHPh_2$	H	**93**	92	99:1	96
Ph	Et	$CHPh_2$	H	**93**	85	88:12	97
2-$MeOC_6H_4$	Me	*t*-Bu	H	**93**	96	80:20	97
2-BrC_6H_4	Me	*t*-Bu	H	**93**	97	99:1	96
Ph	Me	*t*-Bu	Me	**94**	90	99:1	89
4-$MeOC_6H_4$	Me	*t*-Bu	Et	**94**	79	99:1	92
4-ClC_6H_4	Me	*t*-Bu	*n*-Bu	**94**	80	99:1	88

Scheme 39. Reaction of 2-isocyanoacetates with *N*-phosphinoylketimines catalyzed by silver-aminophosphine complexes.



R^1	R^2	R^3	R^4	Cat.	yield (%)	dr	ee (%)
Ph	Me	Me	H	**96**	62	92:8	99
Ph	Et	Me	H	**96**	67	89:11	91
4-$MeOC_6H_4$	Me	Me	H	**96**	68	88:12	98
4-BrC_6H_4	Me	Me	H	**96**	46	81:19	98
Ph	Me	*i*-Pr	Me	**97**	99	98:2	90
Ph	Me	*i*-Pr	*i*-Bu	**97**	78	93:7	80
4-$NO_2C_6H_4$	Me	*i*-Pr	Me	**97**	93	94:6	86

Scheme 40. Asymmetric synthesis of imidazolines catalyzed by metal complexes with cinchona-derived ligands.



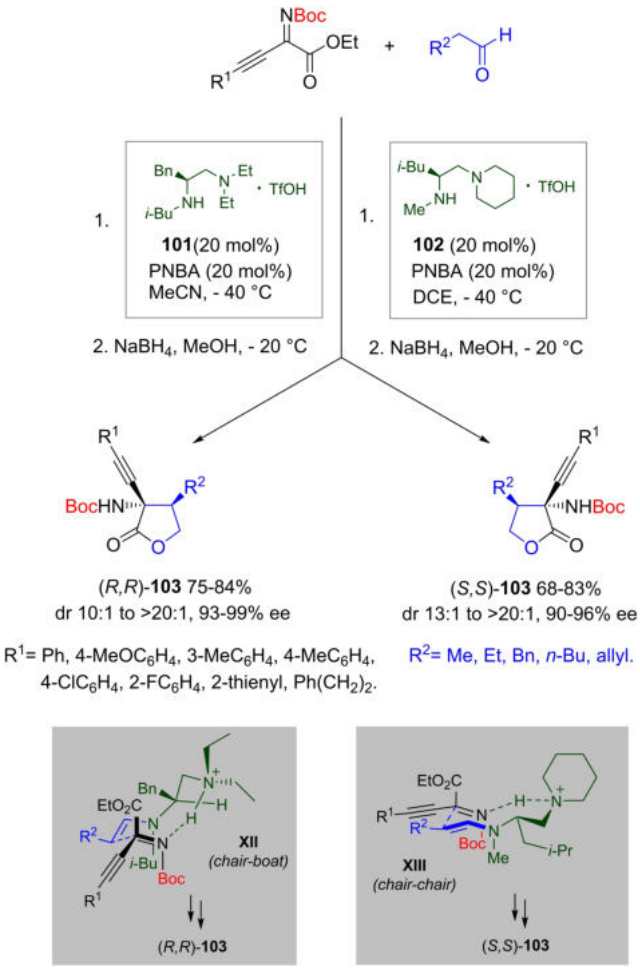
Scheme 41. Enantioselective aza-benzoin reaction of enals and ynals with *N*-*t*-butoxycarbonylketimines under NHC catalysis.

group can be reductively replaced with a hydrogen atom, in this process the TosMIC reagent actually acts as a 2-isocyanoformate synthon.

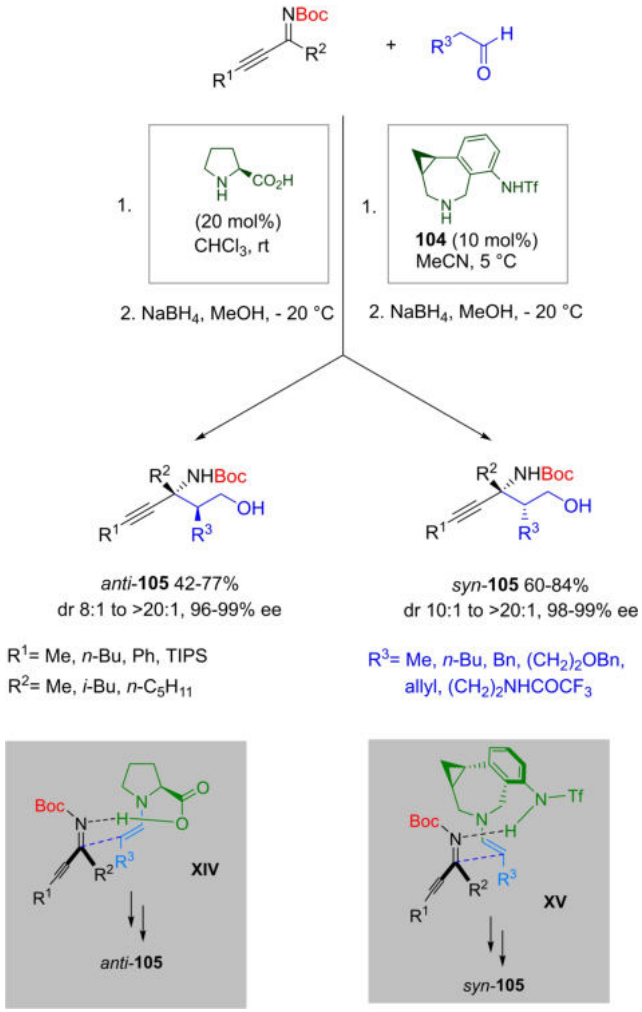
Almost simultaneously, the same process portrayed in Scheme 39 has been developed using similar cinchona-derived ligands **96** or **97** in the presence of copper(II) triflate and nickel(II) chloride respectively (Scheme 40).[73] With these ligand-metal salt combinations a reversed *Re* selectivity is observed for the nucleophilic addition. The chiral copper-**96** complex has been specifically designed for the reaction of 2-isocyanoacetate esters leading to imidazoline derivatives **98** in satisfactory yields and diastereoselectivity but excellent enantioselectivity. Conversely the nickel-**97** complex is more efficient with superior 2-isocyanoalkanoate esters giving products **98** in excellent yields and diastereoselectivity but a slightly lower enantioselectivity. The aza-benzoin reaction of enals and ynals with *N*-*t*-butoxycarbonylketimines efficiently occurs under chiral *N*-heterocyclic carbene catalysis leading to the enantioselective synthesis of α-amino ketone derivatives **100** (Scheme 41).[74] The active catalyst is generated by deprotonation of triazolium salt **99** using cesium(I) carbonate and upon reaction with the α,β-unsaturated aldehydes gives the Breslow intermediate **XI** which regioselectively attacks at C-1 the ketimine. Because of the notable steric hindrance of the nucleophilic center only highly electrophilic ketimines bearing at least one electron-withdrawing group are enough reactive to provide the target compounds. The values of enantiomeric excess recorded for this reaction are generally high and the chemical yields satisfactory except for the use of ynals as reactants (31–37%).

The reaction of simple alkanals with *N*-activated ketimines has been introduced only very recently and applied to the enantiodivergent synthesis of enantiomeric γ-butyrolactones **103** (Scheme 42).[75] The enantioselective Mannich reaction of aldehydes with *N*-*t*-butoxycarbonylalkynylketimino esters occurs under enamine catalysis provided by diamino monotriflate salts **101** and **102** in the presence of *p*-nitrobenzoic acid (PNBA). The lability of the α-stereocenter in the resulting aminoaldehyde makes advisable a prompt reduction of the carbonyl group with sodium borohydride allowing the generated alcohol to spontaneously cyclize to the corresponding lactones **103**.

The origin of the enantiodivergence using the structurally related diamino catalysts **101** and **102** can be rationalized accounting for the different transition states envisaged for the formation of the corresponding adducts. The intermediate enamine formed with catalyst **101** preferentially reacts through a chair-boat transition state **XII** involving a selective attack of the *Si* face of the enamine to the *Re* face of the (*Z*)-ketimine leading after reduction and cyclization to lactone (*R,R*)-**103**. Conversely, the corresponding enantiomer (*S,S*)-**103** is formed exploiting a related process entailing a chair-chair transition state **XIII** privileging the attack of the *Re* face of the enamine to the *Si* face of the ketimine. These assumptions are also corroborated by density functional theory (DFT) calculations regarding the preferred conformation adopted by the enamine intermediates and the energy of the postulated transition states. The viability of this strategy has been also evaluated using *N*-*t*-butoxycarbonyl-alkynyltrifluoromethylketimines ultimately leading after reduction of the amino aldehyde intermediates to the corresponding γ-amino alcohols in good yield and stereoselectivity. Later on, this approach has been extended to the diastereodivergent synthesis of amino alcohol derivatives **105** starting from *N*-*t*-butoxycarbonylalkynylalkylketimines (Scheme 43).[76] The reaction catalyzed by L-proline is assumed to occur *via* the *s-trans* enamine according to the transition state **XIV**.

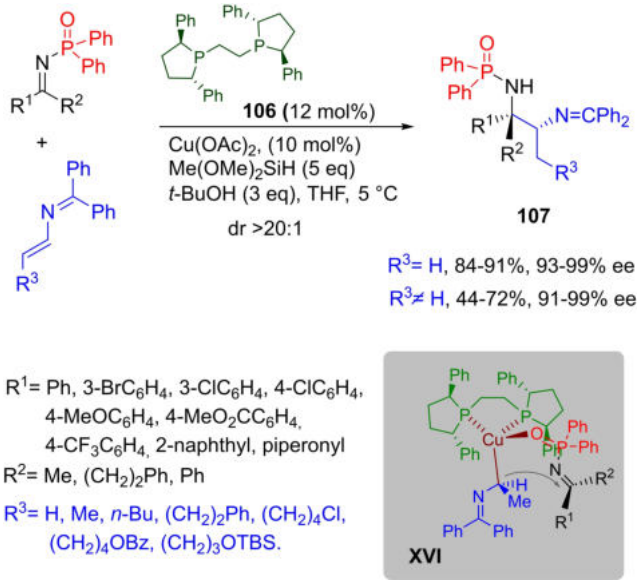


Scheme 42. Enantiodivergent addition of alkanals alkynyl *N*-*t*-butoxycarbonylketimino esters under enamine catalysis.



Scheme 43. Diastereodivergent addition of alkanals to *N*-*t*-butoxycarbonyalkynylketimines under enamine catalysis.

The *Re* face of the enamine selectively adds to the *Re* side of the ketimine leading to γ-amino alcohol *anti*-**105** after the subsequent reduction. The utilization of catalyst **104** leads to the preferential formation of the *s-cis* enamine which attacks by the *Si* face the *Re* face of the ketimine following the transition state **XV**. The corresponding adduct, after carbonyl reduction affords, amino alcohol *syn*-**105**. The results provided by catalyst **104** for the synthesis of the *syn* stereoisomer are generally better than those obtained using L-proline for the preparation of *anti*-**105**. The asymmetric reductive coupling of azadienes with *N*-diphenylphosphinoylketimines represents a very efficient procedure for the preparation of trisubstituted 1,2-diamino derivatives **107** (Scheme 44).[77] The reaction is catalyzed by a chiral copper-diphospholane **106** complex which in the presence of an excess of a silane reductant affords a chiral organocopper intermediate that is able to provide an enantioselective addition to the *Si* face of the ketimine according to the transition state **XVI**. The specific coordinative interaction between the metal and the diphenylphosphinoyl moiety is of fundamental importance since other substrates such as *N*-arylsulfonyl or *N*-*t*-butoxycarbonyl ketimines are totally ineffective in this process. As commonly observed in these addition reactions, unsubstituted azadienes (R^3 = H) provide better yields of the corresponding compounds **107** compared to differently substituted reactants. It is important to remark that this procedure has been considerably inspired by a previous work in which styrene was successfully employed as reactant with three different *N*-diphenylphosphinoylketimines using the same catalyst-reductant combination.[78]

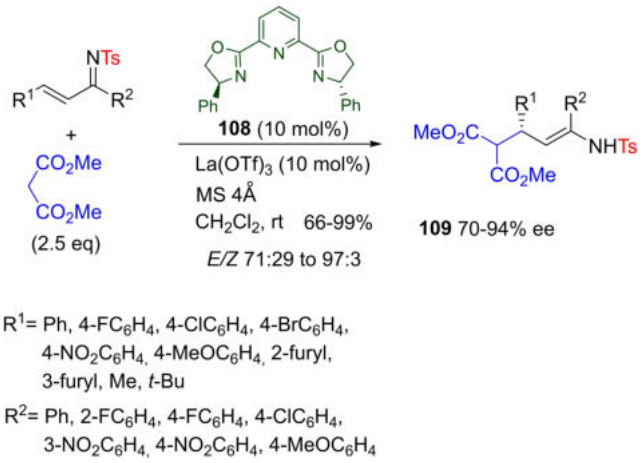


Scheme 44. Asymmetric reductive coupling of azadienes with *N*-diphenylphosphinoylketimines.

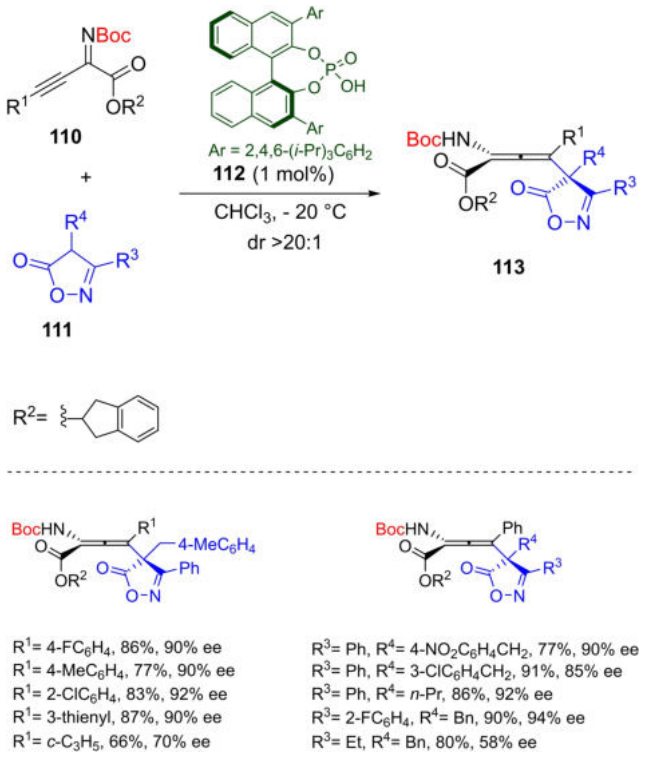
7. Vinylogous Mannich Reactions

The reaction of dimethyl malonate with α,β-unsaturated *N*-tosylketimines catalyzed by the lanthanum complex with PyBOX **108** results in a regioselective 1,4 addition leading to the enamine derivatives **109** (Scheme 45).[79] These compounds are obtained with satisfactory enantioselectivity and *E* diastereoselectivity. Interestingly, malononitrile is totally ineffective in this process since the activation of the malonate ester occurs through the interaction of the oxophilic lanthanum cation with the carboxyl oxygen atoms. A related process has been carried out on β-trifluoromethyl-α,β-unsaturated *N*-tosyl-ketimines using a copper complex with chiral bisoxazoline **108**.[80] The level of stereoselectivity observed in this reaction is similar to that obtained with other α,β-unsaturated ketimines showing a marked preference for the *E* diastereomer.

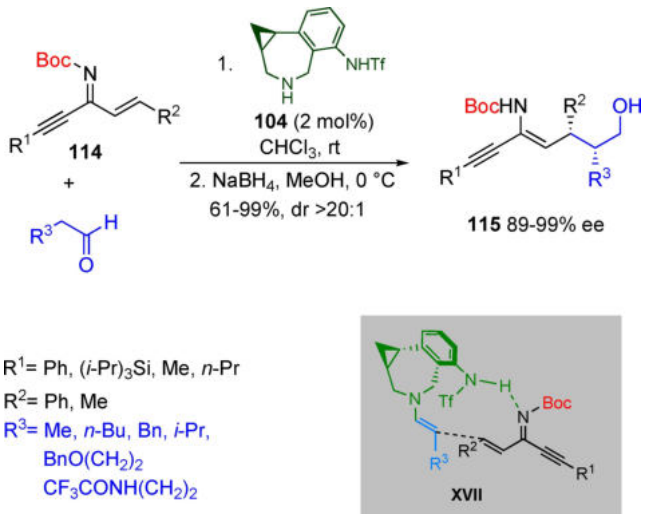
The conjugate addition of isoxazolones **111** to β,γ-alkynyl-α-ketimino esters **110** catalyzed by chiral phosphoric acid **112** affords α-amino allenoates **113** featuring an axially chiral tetrasubstituted allene system in satisfactory yields and good diastereo- and enantioselectivity (Scheme 46).[81] The best values of diastereomeric ratio are obtained using ketimino substrates esterified with 2,3-dihydro-1*H*-inden-2-ol. Ketimino esters embedding aryl and heteroaryl substituents are particularly effective in this reaction which conversely shows modest results with cycloalkanyl groups. Similarly, the presence of 3-alkanyl substituents in isoxazolones **111** provides a notable drop in the enantioselectivity of the process. Aldehyde enolates undergo a regioselective conjugate addition at the double bond in alkenyl alkynyl ketimines **114** using chiral catalyst **104** (Scheme 47).[82] This catalyst was already proved effective for the 1,2-addition of



Scheme 45. Enantioselective conjugate addition of methyl malonate to α,β-unsaturated *N*-tosylketimines.



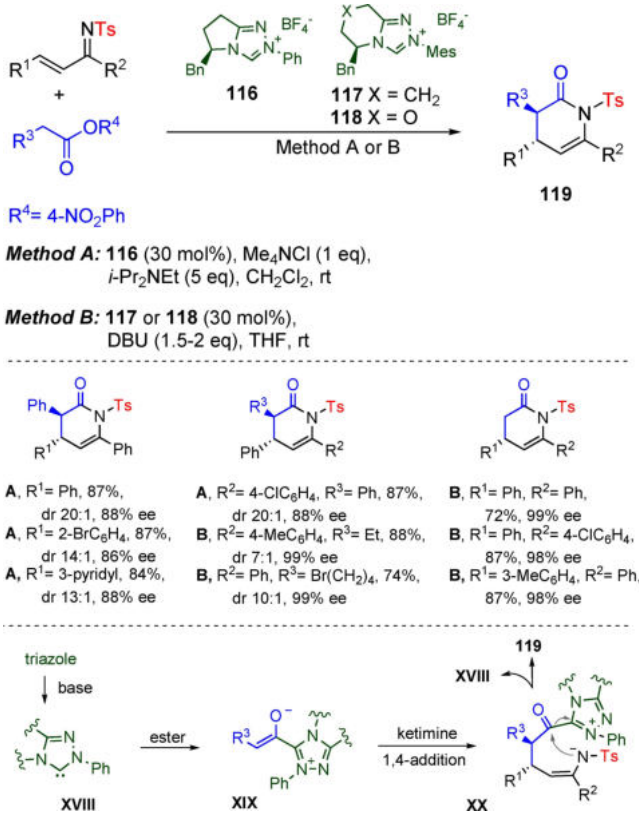
Scheme 46. Asymmetric synthesis of α-aminoallenoates from alkynyl-α-ketimino esters catalyzed by chiral phosphoric acid **112**.



Scheme 47. Diastereo and enantioselective synthesis of enamido alcohols **115** by conjugate addition of aldehydes to alkenyl alkynyl ketimines.

aldehydes to alkynylketimines (Scheme 43) and after reduction of the intermediate enamido aldehyde with sodium borohydride the corresponding *syn* alcohols **115** are obtained in good yields and stereoselectivity. According to the transition state model **XVII**, the *Z*-ketimine **114** is activated by the acidic NH of the catalyst supporting the face selective attack of the enamine moiety to the conjugated double bond.

In the presence of intermediate carbonyls bearing good leaving groups the *N*-substituted enamino derivatives formed by conjugate addition of enolate anions with α,β-unsaturated ketimines promptly undergo to an intramolecular ring closure leading to heterocyclic structures. The utilization of simple esters has been demonstrated in the reaction with α,β-unsaturated *N*-tosylketimines for the preparation of chiral dihydropyridones **119** (Scheme 48). Chiral triazolium salt **116** has been initially devised as the best catalyst for the reaction of arylacetic esters with various ketimines using method A.[83] With this method, the corresponding products **119** are obtained in good yield and diastereoselectivity although the enantioselectivity is not particularly high. The six membered ring homologues **117** and **118** which are particularly suited for the reactions using acetic and alkanoic esters following method B afford dihydropyridones **119** in high yield and excellent stereoselectivity.[84] The whole process entails the generation of a *N*-heterocyclic carbene (NHC) **XVIII** by deprotonation of the triazolium salt which subsequently reacts with the ester leading to a zwitterionic enolate anion **XIX**. The latter nucleophilic

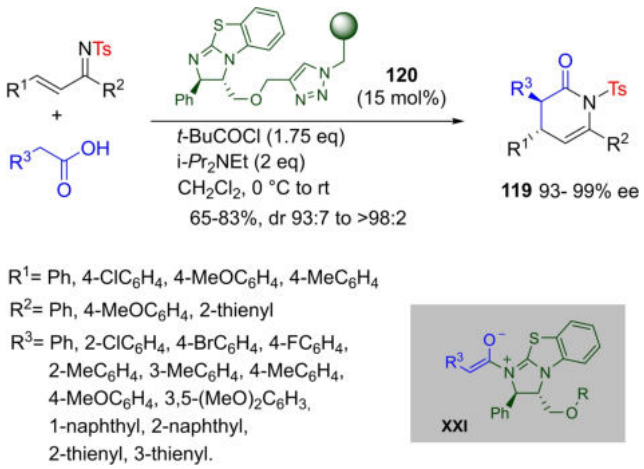


Scheme 48. Asymmetric synthesis of dihydropyridones by tandem conjugate addition-lactamization.

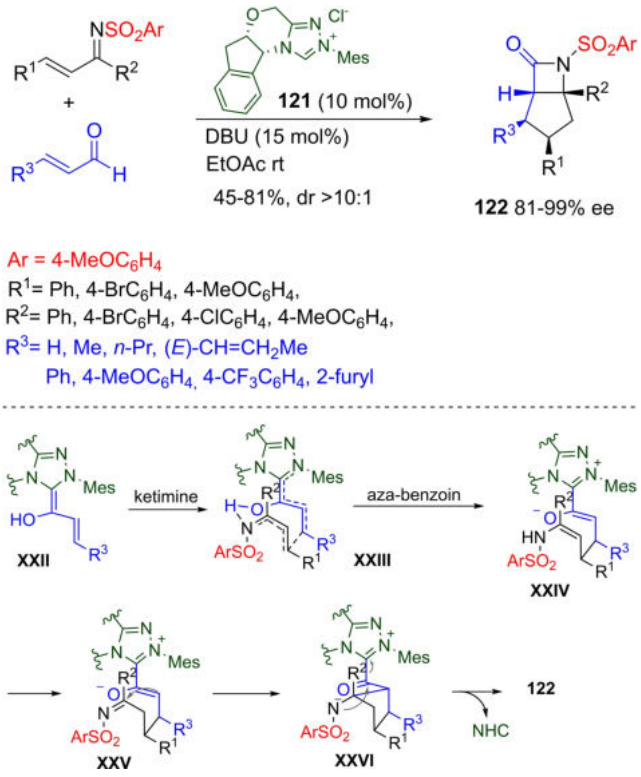
intermediate gives the Michael adduct **XX** in the reaction with the ketimine and finally by an intramolecular ring closure affords the target dihydropyridones **119** regenerating the catalytic system **XVIII**.

Carboxylic acids can also be used in a related synthetic approach providing that they are *in situ* converted into a mixed anhydride using pivaloyl chloride. The most effective catalyst is a polystyrene resin-bound chiral benzotetramisole **120** which acts converting the mixed anhydride into an acylammonium enolate anion **XXI** capable to react with the α,β-unsaturated *N*-tosylketimine (Scheme 49).[85] The corresponding dihydropyridones **119** are generated in good yield and stereoselectivity following the mechanism previously described for the NHC-catalyzed reaction. The catalyst can be easily recovered from the reaction mixture by simple filtration and promptly reused several times with comparable performances. Notably, the reaction can also be carried out exploiting a continuous flow process experiencing even a superior level of enantioselectivity compared to the batch conditions. A formerly appeared procedure using a chiral betramine catalyst working under homogeneous conditions was also quite effective in giving compounds **119** but with a lower diastereomeric ratio.[86]

The reaction between enals and α,β-unsaturated *N*-arylsulfonylketimines catalyzed by the *N*-heterocyclic carbene (NHC) precursor **121** affords bicyclic azetidinones **122** in satisfactory yields and high diastereo- and enantioselectivity (Scheme 50).[87] The Breslow intermediate **XXII**, formed upon reaction of the the enal with the chiral NHC generated from **121**, reacts with the ketimine through a transition state **XXIII** leading to the aza-benzoin adduct **XXIV**. After tautomerization of the enamine moiety, the resulting ketimine **XXV** undergoes an intramolecular Mannich reaction generating the five membered carbacyclic unit



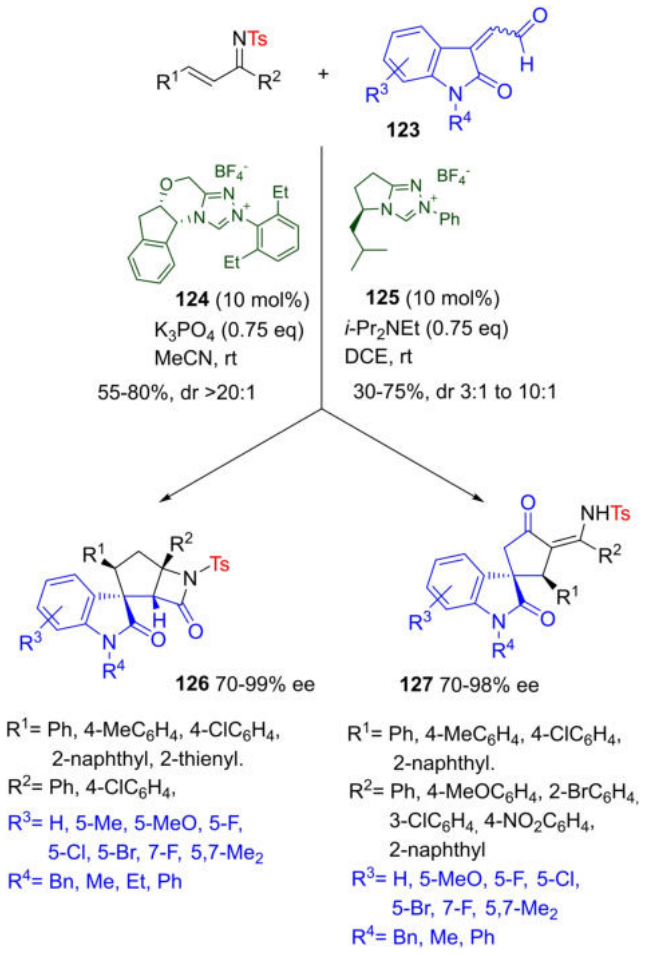
Scheme 49. Asymmetric synthesis of dihydropyridones by tandem conjugate addition-lactamization.



Scheme 50. Synthesis of bicyclic azetidinones by asymmetric aza-benzoin reaction.

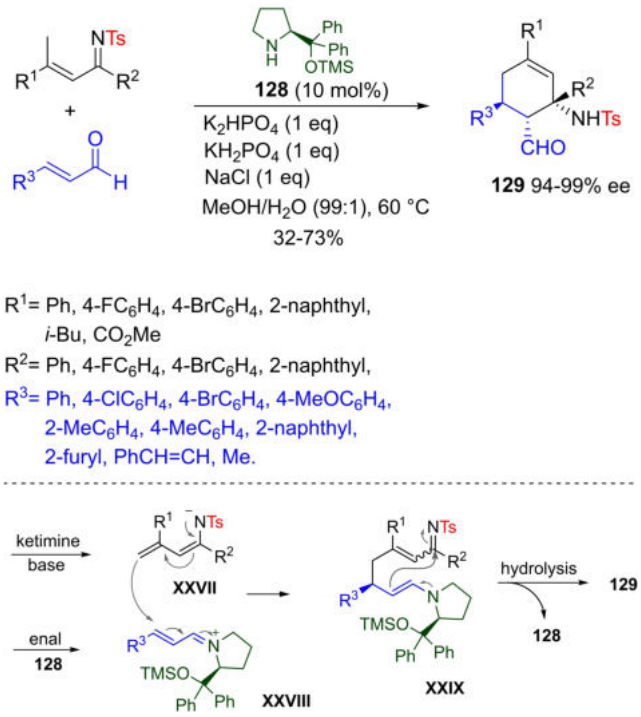
XXVI. The final lactamization of this intermediate affords the target bicyclic compounds **122** and regenerates the NHC catalyst. Later on, a related process has been developed on isatin-derived enals **123** using NHC precursors **124** and **125** (Scheme 51).[88] Triazole precatalyst **124** structurally related to **121** gives the spirotetracyclic azetidinones **126** in good yield and satisfactory stereoselectivity following the same mechanism portrayed in Scheme 50. The utilization of precatalyst **125** leads to the preferential formation of the spiro derivative **127** arising from the intramolecular reaction between the *N*-tosyl enamine and the acyl moiety. The latter process generally shows a lower level of efficiency compared to the former one. The reaction of enals with β-disubstituted α,β-unsaturated ketimines catalyzed by chiral pyrrolidine **128** follows an umpoled pathway leading to the highly stereoselective synthesis of 2-amino carbaldehyde derivatives **129** (Scheme 52).[89] Under basic conditions, the ketimine undergoes a γ-deprotonation leading to azadienolate **XXVII** which reacts with the chiral vinylogous iminium ion **XXVIII**. The enamino moiety of the resulting Michael adduct **XXIX** reacts with the ketimine leading to the target carbaldehyde **129** after hydrolytic regeneration of the catalyst.

The aza-Rauhut-Currier reaction of α,β-unsaturated *N*-arylsulfonylketimino esters with enones catalyzed

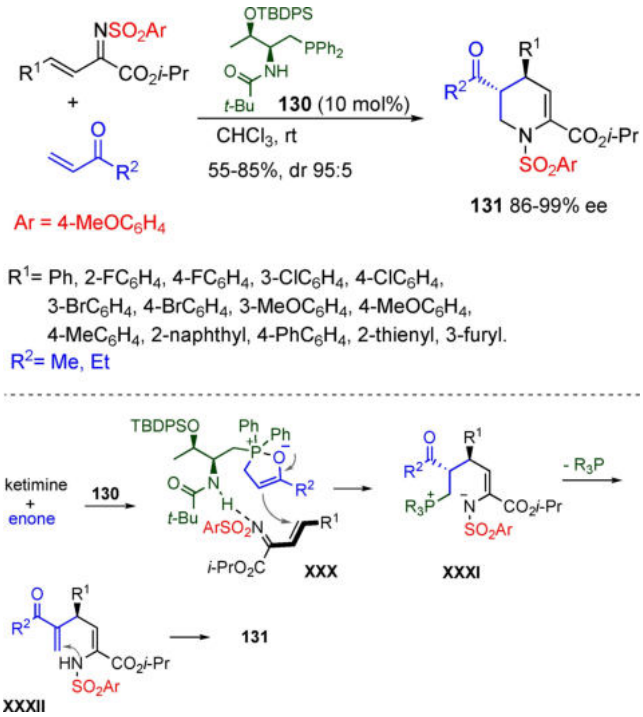


Scheme 51. Regiodivergent asymmetric reaction of isatin-derived enals and α,β-unsaturated ketimines.

by chiral phosphine **130** provides a direct entry to optically active tetrahydropyridine derivatives **131** (Scheme 53).[90] The ester function in the ketimine substrate is instrumental in order to achieve satisfactory levels of stereoselectivity considering that common α,β-unsaturated ketimines give moderate values of diastereo- and enantioselectivity even using other chiral phosphine catalysts.[91] Upon conjugate addition of the chiral phosphine with the enone, the zwitterionic enolate anion formed reacts with the ketimino ester according with transition state **XXX**. The obtained intermediate **XXXI** eliminates the phosphine catalyst regenerating the enone system **XXXII** which upon an intramolecular aza-Michael ring closure affords the tetrahydropyridine product **131**. Recently, a particularly hindered chiral phosphine catalyst **132** has been devised for the aza-Rauhut–Currier reaction of enones with β-perfluoroalkyl-α,β-unsaturated *N*-arylsulfonylketimines (Scheme 54).[92] The corresponding tetrahydropyridines **133** are obtained in good yield and excellent stereoselectivity.

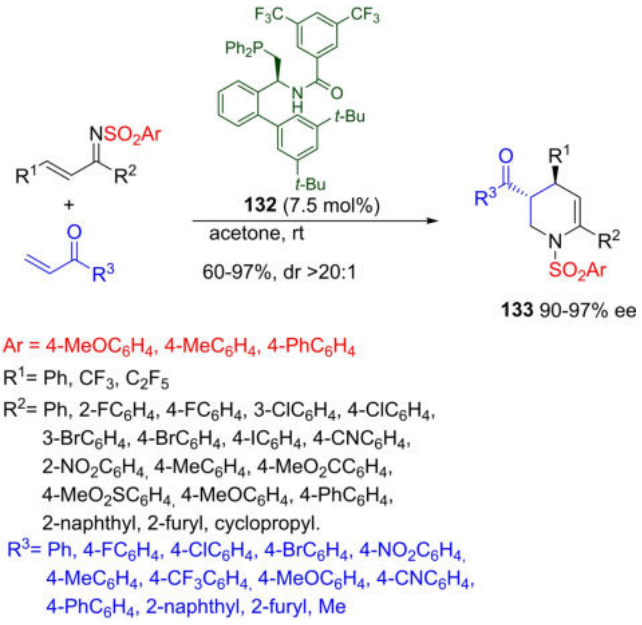


Scheme 52. Enantioselective synthesis of 2-amino carbaldehydes catalyzed by chiral pyrrolidine **128**.



Scheme 53. Asymmetric aza-Rauhut-Currier reaction catalyzed by chiral phosphine **130**.

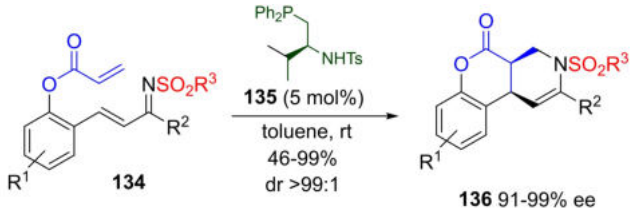
The intramolecular version of this process has been realized using as substrates phenolic acrylates embed-



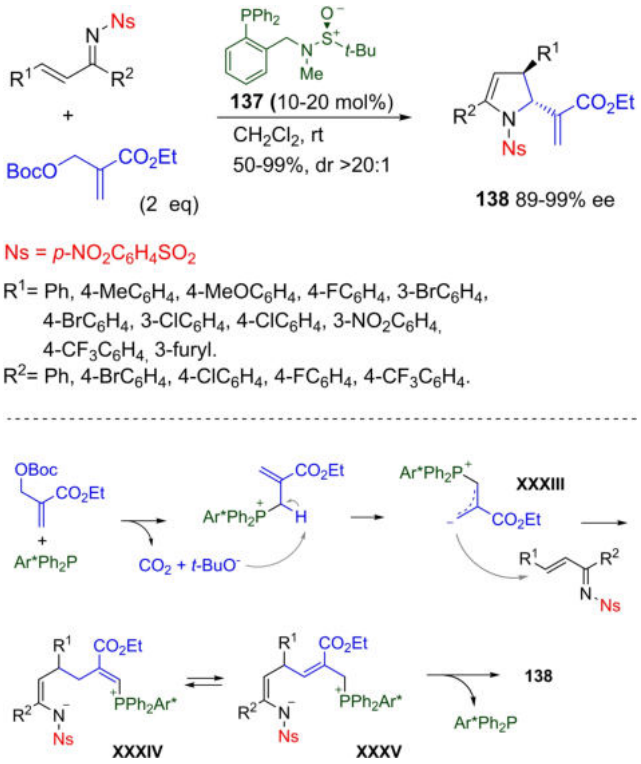
Scheme 54. Enantioselective synthesis of tetrahydropyridines by aza-Rauhut–Currier reaction catalyzed by chiral phosphine **132**.

ding the α,β-unsaturated ketimine moiety **134** in the presence of chiral phosphine **135** (Scheme 55).[93] The expected tricyclic derivatives **136** are obtained as single diastereomers with excellent levels of enantioselectivity.

A very interesting protocol has been recently devised for the efficient diastereo- and enantioselective synthesis of functionalized pyrrolines **138** (Scheme 56).[94] This approach is based on the 1,4-regioselective addition of an ester enolate to a α,β-unsaturated *N*-nosylketimine catalyzed by phosphine **137** embedding a chiral sulfoxyamino group. The zwitterionic nucleophile **XXXIII** is generated by a



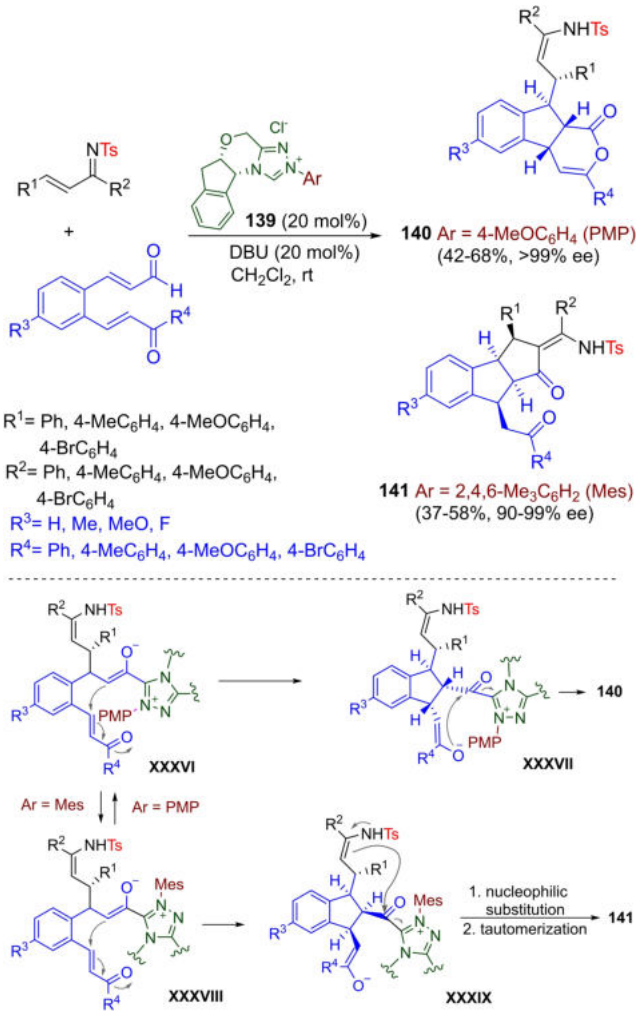
Scheme 55. Intramolecular asymmetric aza-Rauhut–Currier reaction catalyzed by chiral phosphine **135.**



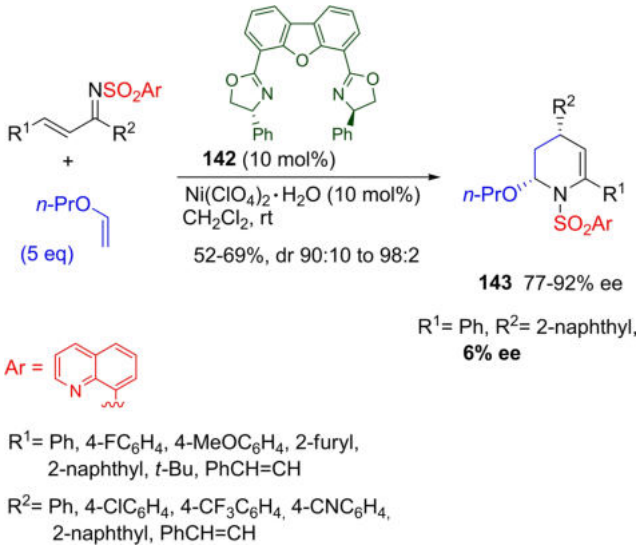
Scheme 56. Enantioselective synthesis of 2-pyrrolines catalyzed by chiral phosphine **137**.

conjugate addition of the chiral phosphine to the allylic carbonate. A further Michael addition of **XXXIII** to the ketimine affords intermediate **XXXIV** which is in equilibrium with its regioisomer **XXXV** that undergoes a ring closure leading to the final product **138** regenerating the phosphine catalyst.

The reaction of 2-aroylvinylcinnamaldehydes with α,β-unsaturated *N*-tosylketimines in the presence of triazolium ion precatalyst **139** provides an interesting example of a process in which the structure of the final products is affected by the stereoselectivity of the first ring closure. (Scheme 57).[95] According to the nature of the *N*-aryl substituent in the precatalyst **139**, the conformational equilibrium can be shifted between intermediates **XXXVI** and **XXXVIII**. Ring closure of intermediate **XXXVI** bearing a *N*-*p*-methoxyphenyl group (PMP) ensures the preferential formation of stereoisomer **XXXVII** which undergoes a further intramolecular reaction involving the oxygen atom of the enolate anion. This process selectively affords lactone **140** in satisfactory yield and high enantioselectivity. Conversely, ring closure of intermediate **XXXVIII** bearing a *N*-mesityl group (Mes) generates a different stereoisomer **XXXIX** in which the reaction of the enamino moiety with the carbonyl group is favored. The latter process selectively generates tricyclic compound **141** with a comparable level of efficiency.



Scheme 57. Regiodivergent enantioselective synthesis of polycyclic derivatives catalyzed by NHC precursor **139**.

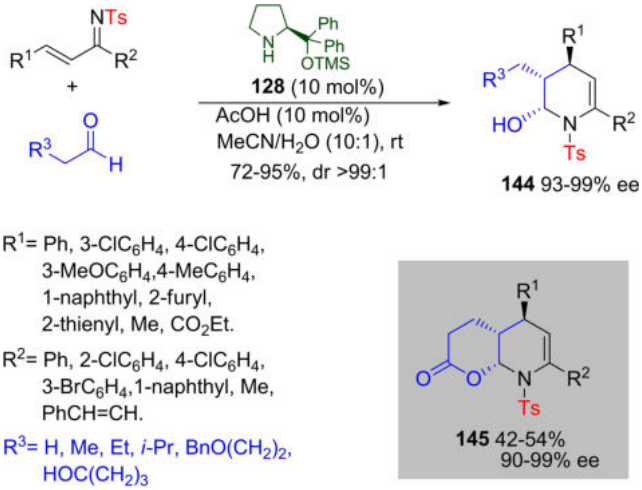


Scheme 58. Enantioselective Diels-Alder reaction of *n*-propyl vinyl ether with α,β-unsaturated ketimines.

8. Diels-Alder Reactions

The cycloaddition reaction of α,β-unsaturated *N*-tosylketimines with electron-rich alkenes can be classified as an inverse-electron-demand aza-Diels-Alder process. The first reported example of Diels-Alder reaction of α,β-unsaturated *N*-arylsulfonylketimines with enolethers was catalyzed by the nickel complex with chiral bisoxazoline ligand **142** (Scheme 58).[96]

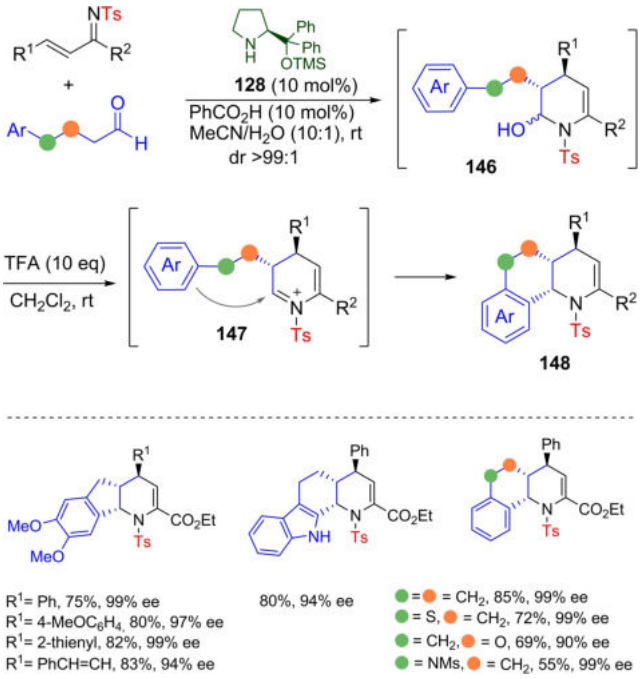
As previously demonstrated, nitrogen-containing heteroaryl groups in the sulfonyl moiety are mandatory for an appropriate reaction with organometallic complexes. In this context, the common *p*-tolyl group is totally ineffective but good results are obtained using the 8-quinolyl system. Similarly, propylvinyl ether gave the best performances among different alkylvinyl ethers tested for this purpose. The tetrahydropyridine derivatives **143** are usually obtained in satisfactory yield and stereoselectivity except when a notable steric crowding is present around the imino group as witnessed by the disappointing result evidenced in the utilization of the ketimine bearing a 2-naphthyl substituent. The reaction of *N*-activated ketimines with aldehydes catalyzed by chiral pyrrolidine **128** is supposed to occur *via* the corresponding enamine which is the actual dienophile involved in the process (Scheme 59).[97] The cyclic hemiaminals **144** are formed with outstanding regio- and stereoselectivity after hydrolysis of the aminal intermediate which allows the regeneration of the organocatalyst. The utilization of glutaraldehyde in the same process allows the formation of the corresponding unstable lactols which upon oxidation with 2-iodoxybenzoic



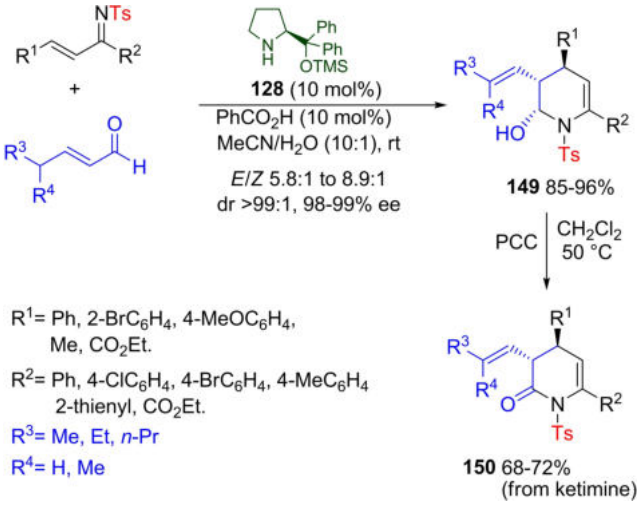
Scheme 59. Enantioselective synthesis of hemiaminals **144** organocatalyzed by chiral pyrrolidine **128**.

acid (IBX) finally afford lactones **145** in overall moderate yield but high enantioselectivity.[98]

Aldehydes bearing an aryl or heteroaryl appendage in terminal position upon reaction with α,β-unsaturated *N*-tosylketimines in the presence of chiral pyrrolidine **128** afford the expected cyclic hemiaminals **146** (Scheme 60).[99] Upon acid treatment of the crude products **146** the *N*-tosyliminium ion **147** thus generated undergoes an intramolecular Friedel–Crafts reaction with the aryl ring leading to tricyclic derivatives



Scheme 60. Asymmetric synthesis of tetrahydropyridine derivatives **148**.

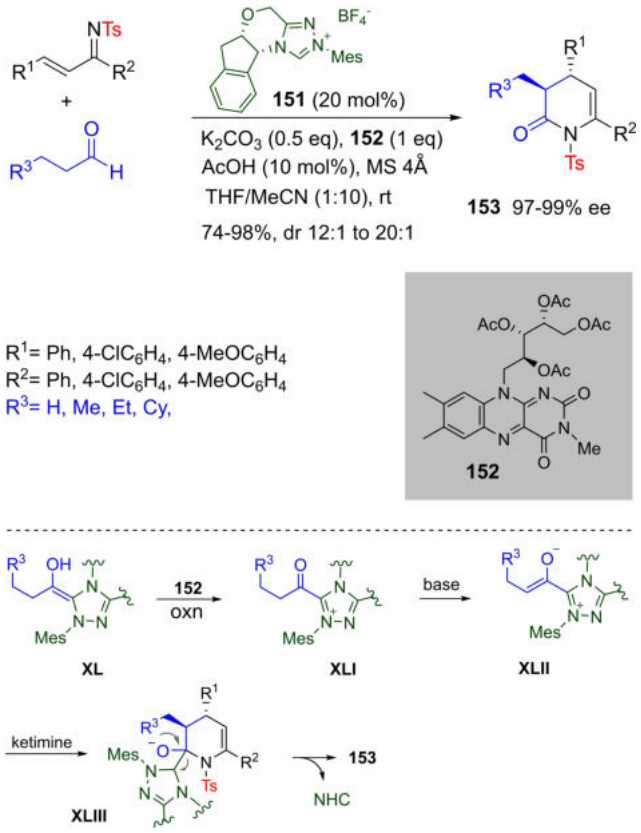


Scheme 61. Two-step enantioselective synthesis of dihydropyridin-2-ones **150**.

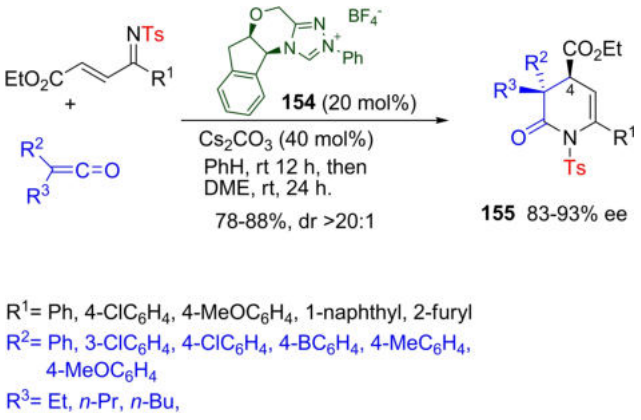
148. The versatility of this process is witnessed by the large variety of products obtainable using aldehydes embedding common heteroatoms in their structure. The reaction of enals with α,β-unsaturated *N*-tosylketimines in the presence of chiral pyrrolidine catalyst **128** entails the formation of a chiral dienamine intermediate which upon a α-regioselective Diels-Alder cycloaddition affords hemiaminals **149** (Scheme 61).[100]

This process is featured by a satisfactory level of *E* diastereoselectivity and excellent values of diastereo- and enantioselectivity for the C-sp^3 stereocenters. The regiochemical outcome observed using crotonaldehyde is strongly affected by the nature of the ketimine employed in this process. α-Ketimino esters ($R^2 = CO_2Et$) react showing the usual α-regioselectivity leading to compounds **149**. Conversely, γ-ketimino esters ($R^1 = CO_2Et$) exclusively afford products arising from a cycloaddition involving the terminal double bond of the dienamine intermediate (γ-attack). The latter products are formed in satisfactory yields but rather low enantioselectivity probably because of the less effective stereoinductive effect exerted by the catalyst stereocenter. This procedure can also be adapted to the preparation of chiral dihydropyridinones **150** by *in situ* oxidation of hemiaminals **149** with pyridinium chlorochromate. As previously described, enolate anions can also be generated under chiral *N*-heterocyclic carbene (NHC) catalysis. These anions are effective dienophiles in Diels-Alder cycloadditions as demonstrated in the reaction of aldehydes with α,β-unsaturated *N*-tosylketimines catalyzed by chiral triazole precatalyst **151** (Scheme 62).[101] The actual enolate species is generated by preliminary formation of the enol **XL** by reaction of the NHC with the aldehyde followed by oxidation to the triazolyl ketone **XLI** using riboflavin derivative **152**. Enolate anion **XLII** obtained under basic conditions then reacts with the ketimine leading to cycloadduct **XLIII** which upon elimination of the NHC affords the dihydropyridinone **153** in generally good yield ad excellent stereoselectivity. A related process has been carried out on 2-chloroaldehydes using the same precatalyst and similar reaction conditions but the corresponding dihydropyridinones are obtained only with moderate enantioselectivity.[102]

The oxidation step required in order to generate the enolate **XLII** can be avoided using ketenes as carbonyl reagents in the reaction with γ-ketimino esters in the presence of chiral triazole precatalyst **154** (Scheme 63).[103] The reaction is carried out in benzene at room temperature evidencing satisfactory levels of diastereo- and enantioselectivity. However, the diastereoselectivity of compounds **155** can be greatly enhanced to a value of dr >20:1 just adding 1,2-dimethoxyethane (DME) after 12 h and continuing the stirring for further 24 h. The increased solubility of the solid base in DME is probably responsible for the



Scheme 62. Enantioselective synthesis of dihydropyridin-2-ones **153**.



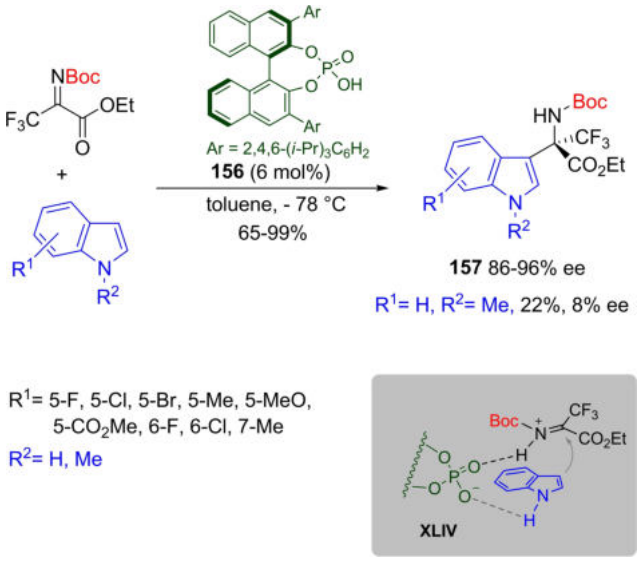
Scheme 63. Asymmetric cycloaddition of ketenes with γ-ketimino esters under chiral NHC catalysis.

thermodynamic C-4 epimerization although in some examples a slight erosion of the enantioselectivity has been observed.

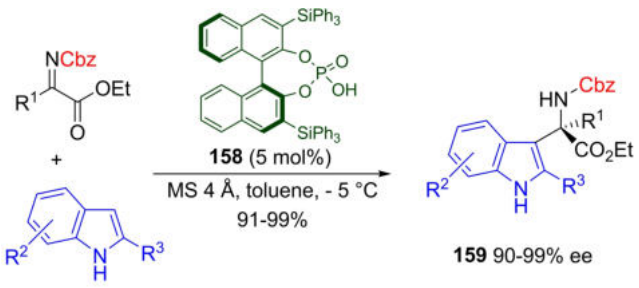
9. Reaction with Aromatic Heterocycles

The enantioselective Friedel-Crafts (F-C) reaction of electron-rich heterocyclic systems to activated ketimines is presently limited to indole and furan derivatives. These processes are catalyzed by chiral Brønsted acids currently available for related transformations such as phosphoric acid **156** which is effective in the reaction of a trifluromethylated ketimino ester with substituted indoles (Scheme 64).[104] The obtained yield and enantioselectivity of adducts **157** are generally good with the notable exception of 1-methylindole which gives rather disappointing results. This behavior is in agreement with many related F–C reactions catalyzed by Brønsted acids in which the presence of the NH group in the indole is mandatory for an appropriate reactivity as tentatively reported in the transition state **XLIV**.

The same trend can be evidenced in the reaction of *N*-benzyloxycarbonylketimino esters with indoles catalyzed by chiral phosphoric acid **158** (Scheme 65).[15] Excellent results are obtained in the formation of compounds **159** using these reaction conditions allowing the process to be carried out at higher temperature. The utilization of *N*-*t*-butoxycarbonylketimino esters is also possible but compounds **159** are obtained with reduced enantiomeric excesses (81–85%). The presence of the free NH group is also required for a viable process. A common feature of several processes carried out using chiral phosphoric acids is the concomitant utilization of molecular sieves in the reaction mixture. This requirement is probably associated to the disruption of the tight hydrogen bonding interactions between the catalyst and reactants caused by water. A different mechanistic pathway seems effective in the reaction of different *N*-benzylindoles with *N*-tosylketimines catalyzed by binaphthyl-derived disulfonic acid monopotassium salt **160**



Scheme 64. Enantioselective F-C reaction of indoles with trifluoromethyl ketimino esters.

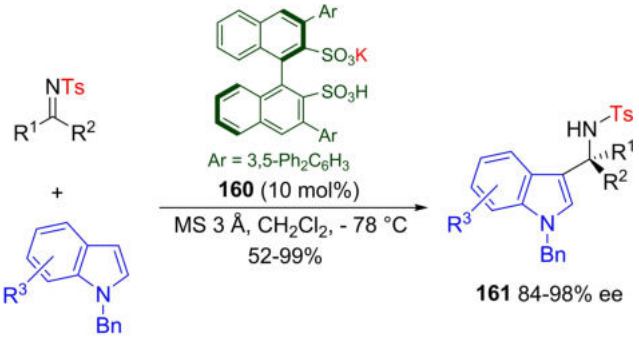


R^1= Ph, 4-BrC_6H_4, 4-MeC_6H_4, 3- $MeOC_6H_4$, 4-$MeOC_6H_4$,
R^2= H, 5-MeO, 6-Me, 6-Cl, 6-Br, 7-Me
R^3= H, Me

Scheme 65. Enantioselective F-C reaction of indoles with α-ketimino esters catalyzed by chiral phosphoric acid **158**.

(Scheme 66).[105] Compared to phosphoric acids, disulfonic acids are endowed of a superior Brønsted acidity, which can be further modulated converting them into monoalkali salts. The cation in catalyst **160** is supposed to coordinate the two sulfonic groups and the activation is limited to the ketimine substrate establishing a strong hydrogen bonding with the nitrogen or the sulfonyl oxygen atoms. As a matter of fact, *N*-benzylated indoles are the preferred reactants in this process. Interestingly, in large scale reactions (up to 5 mmol), the catalyst charge can be lowered to 0.3–1 mol% providing that a small amount of acetic acid (10 mol%) is used as an additive.

The F-C reaction of 4-aminoindoles with *N*-*t*-butoxycarbonylketimino esters can be driven towards

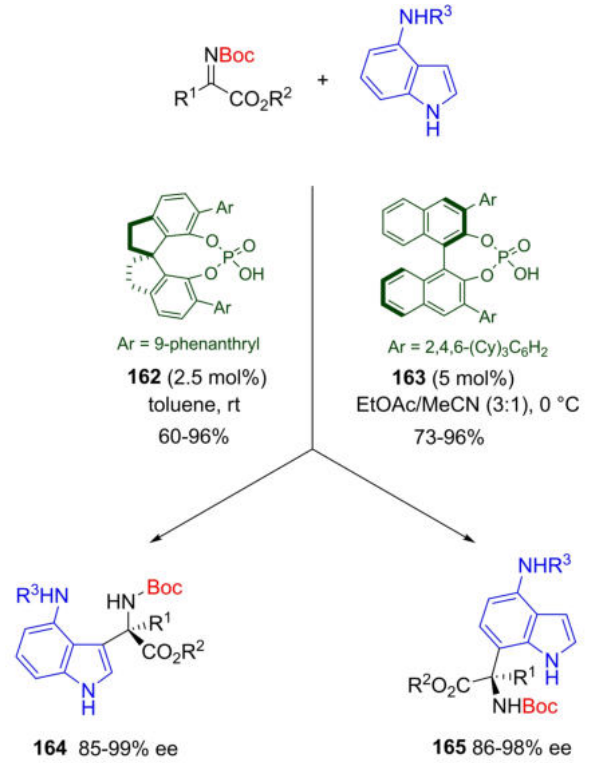


R^1= Ph, 2-BrC_6H_4, 4-BrC_6H_4, 4-FC_6H_4, 4-IC_6H_4, 2-MeC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-naphthyl, 2-furyl, 2-thienyl, 3-thienyl, 2-thionaphthyl
R^2= Me, Et, *n*-Pr,
R^3= H, 4-MeO, 5-MeO, 5- BnO, 6-MeO, 7-MeO

Scheme 66. Enantioselective F-C reaction of indoles with *N*-tosylketimines catalyzed by chiral disulfonic acid monopotassium salt **160**.

the C-3 substituted products **164** or the C-7 regioisomers **165** depending on the nature of the chiral catalyst and conditions employed (Scheme 67).[106] The utilization of SPINOL-derived catalyst **162** in toluene almost exclusively leads 3-substituted indoles **164**. Conversely, BINOL-derived phosphoric acid **163** in a mixture of ethyl acetate and acetonitrile affords the corresponding 7-amino ester derivatives **165**. It is assumed that polar solvents would privilege the F-C reaction at the less hindered 7 position because of the hydrogen bonding network around the catalyst acidic site.

On the other hand, apolar solvents would enhance the reactivity of the ketimine allowing a faster reaction with the more nucleophilic 3 position of the indole. Differently from 2-trialkylsilyloxyfurans which act as dienolate systems in Lewis acid catalyzed reactions (*cf* Scheme 30), 2-methoxyfuran reacts with ketimino esters through a F–C process retaining the structure of



R^1= Me, Ph, 4-MeC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 4-FC_6H_4, 4-BrC_6H_4, 3,4-$Cl_2C_6H_3$, 2-tyhienyl, phenylethynyl
R^2= Me, Et, Bn, *t*-Bu
R^3= Bn, *n*-Bu, 4-$BrC_6H_4CH_2$, EtO_2CCH_2, $CNCH_2$, allyl, propargyl

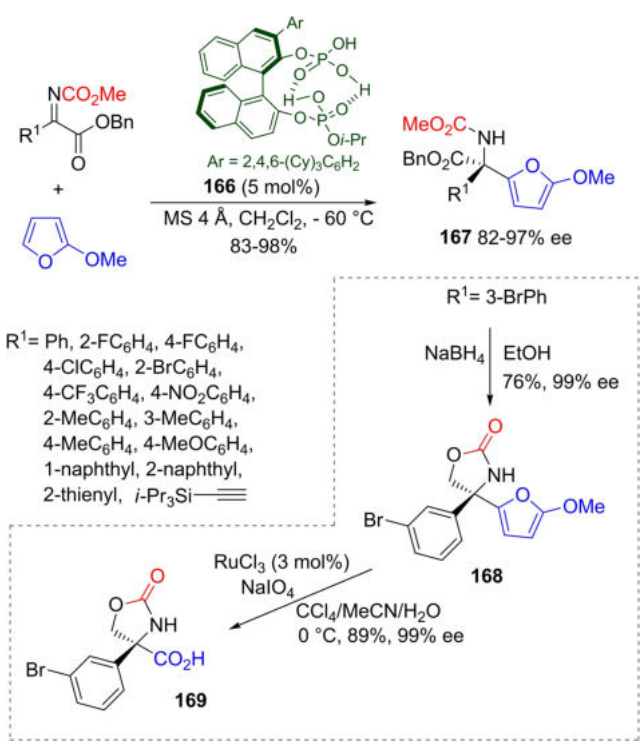
R^1= Ph, 3-ClC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-BrC_6H_4, 3,4-$Cl_2C_6H_3$, 2-tyhienyl, phenylethynyl
R^2= Me, Et, Bn, *t*-Bu
R^3= Bn, *n*-Bu, allyl, propargyl

Scheme 67. Regiodivergent asymmetric synthesis of α-indolyl-α-amino ester derivatives **164** and **165**.

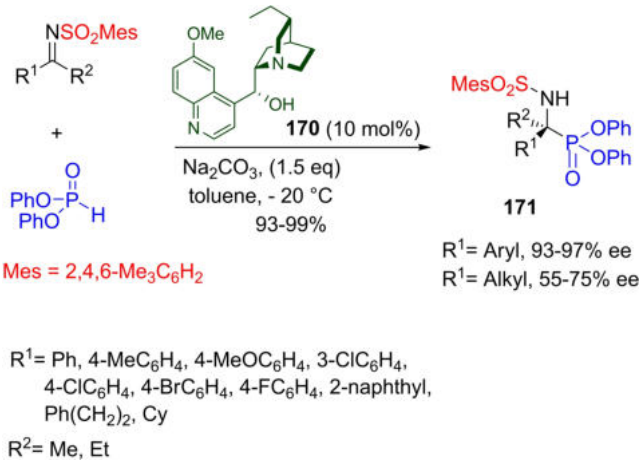
the heterocyclic ring (Scheme 68).[107] After extensive studies, the C_1-symmetric chiral bisphosphoric acid **166** was found the most effective catalyst to obtain adducts **167** in high yield and enantioselectivity. The intramolecular hydrogen bond network between the phosphoric groups enhances the acidity of the catalyst allowing a superior performance over related Brønsted acids in the F-C process. The synthetic versatility of the furan ring as precursor of different structural moieties has been demonstrated converting one of the obtained adducts bearing the 3-bromophenyl substituent into a serine derivative **169**. Chemoselective reduction of the ester group followed by ring closure gave 1,3-oxazolidinone **168** which upon oxidative demolition of the furan ring led to the target amino acid **169** with full retention of the original stereochemistry. Recently this approach has been also extended for the reaction with indoles and pyrroles evidencing a similar level of efficiency.[108]

10. Reaction with Heteronucleophiles

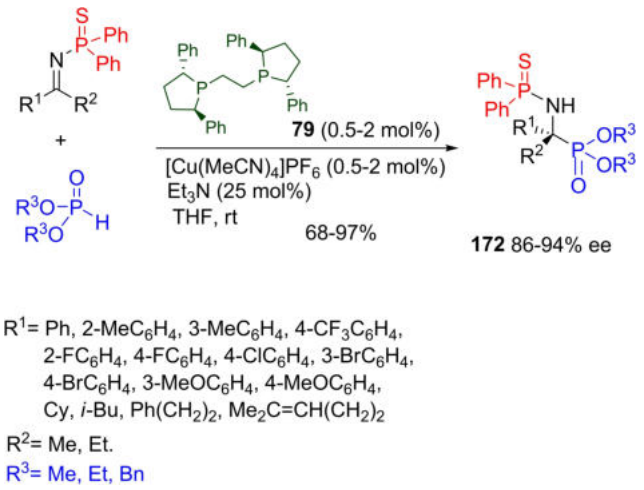
Hydrophosphonylation of imino derivatives represents a direct approach to the synthesis of α-aminophosphonic acid derivatives which can be used as surrogates of their carboxylic analogues in medicinal chemistry.[109] The addition of diphenyl phosphite to *N*-mesitylsulfonylketimines in the presence of hydroquinine **170** affords (*S*)-α-aminophosphonate derivatives **171** in high yield (Scheme 69).[110] The observed enantioselectivity is excellent for arylalkyl ketimines but rather modest for dialkyl ketimines. Access to the *R* enantiomer is possible under the same reaction conditions and with a similar level of efficiency using the hydroquinidine pseudoenantiomer as catalyst. The substrate limitation previously observed does not apply in the reaction of phosphite diesters with *N*-thiophosphonyl ketimines in the presence of copper-phospholane **79** complex (Scheme 70).[111] Under these conditions, a satisfactory enantioselectivity for the synthesis of α-aminophosphonate derivatives **172** is recorded also for dialkyl ketimines. This procedure has been validated for the large scale preparation of a single α-aminophosphonate ester, evidencing simplified reaction conditions that avoid the utilization of



Scheme 68. Enantioselective addition of ketimino esters to 2-mehoxyfuran and application to the synthesis of serine derivative **169**.



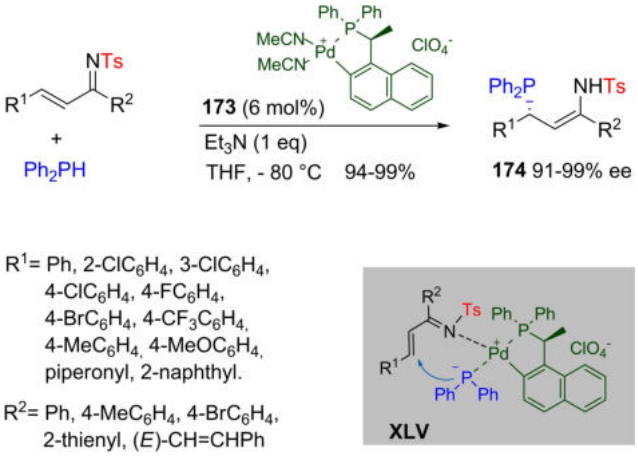
Scheme 69. Asymmetric hydrophosphonylation of *N*-arylsulfonylketimines catalyzed by hydroquinine.



Scheme 70. Enantioselective addition of dialkyl phosphites to *N*-thiophosphonylketimines catalyzed by a copper-phospholane complex.

any solvent and an almost quantitative recovery of the catalyst. Bifunctional iminophosphoranes of type **54** have been used as catalysts in the reaction of *N*-diphenylphosphinoyl- ketimines with diethyl phosphite leading to the corresponding α-aminophosphonates in excellent yields but rather modest enantioselectivity (41–71% ee).[112]

The asymmetric reaction of α,β-unsaturated *N*-tosylketimines with diphenylphosphine in the presence of chiral palladacycle complex **173** occurs in a 1,4 regioselective fashion leading to enaminophosphines **174** in high yields and excellent enantioselectivity (Scheme 71).[113] The acetonitrile ligands in the catalyst are substituted by the interaction with the ketimine nitrogen and the phosphine. Subsequent deprotonation of the phosphine group by triethylamine generates the corresponding anion **XLV** which by an intramolecular conjugate addition affords the optically active enaminophosphines **174**.



Scheme 71. Enantioselectie conjugate addition of diphenyl phosphine to α,β-unsaturated *N*-tosylketimines.

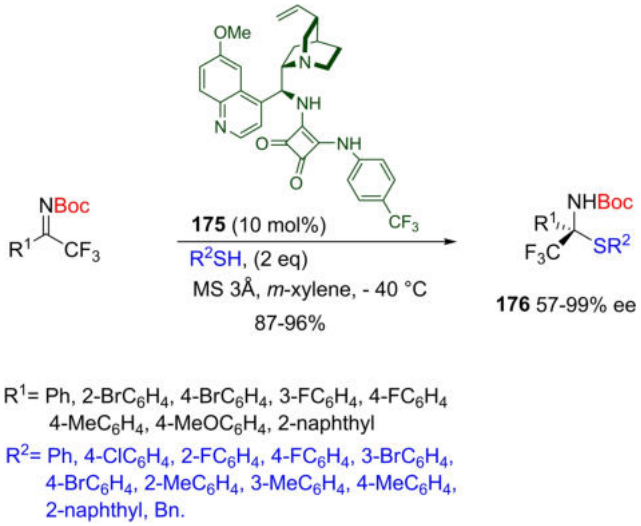
The reaction of various thiols with *N*-*t*-butoxycarbonyltrifluoromethylarylketimines is efficiently catalyzed by chiral squaramide **175** (Scheme 72).[114] The resulting optically active *N,S*-acetal derivatives **176** are formed in good yield and satisfactory enantioselectivity. A lower ee value is obtained using benzyl thiol as reactant (57% ee).

The conjugate protosilylation of α,β-unsaturated tosyl ketimines is catalyzed by the copper complex with chiral bisoxazoline ligand **177** (Scheme 73).[115] Dimethylphenylsilylpinacolborane is able to generate a silylated copper species with the catalyst which can enantioselectively release the silyl nucleophile to the *Re* face of the ketimine according to the plausible transition state **XLVI**. The obtained *N*-tosylenamines **178** are usually formed with excellent *E* diastereoselectivity and good enantioselectivity.

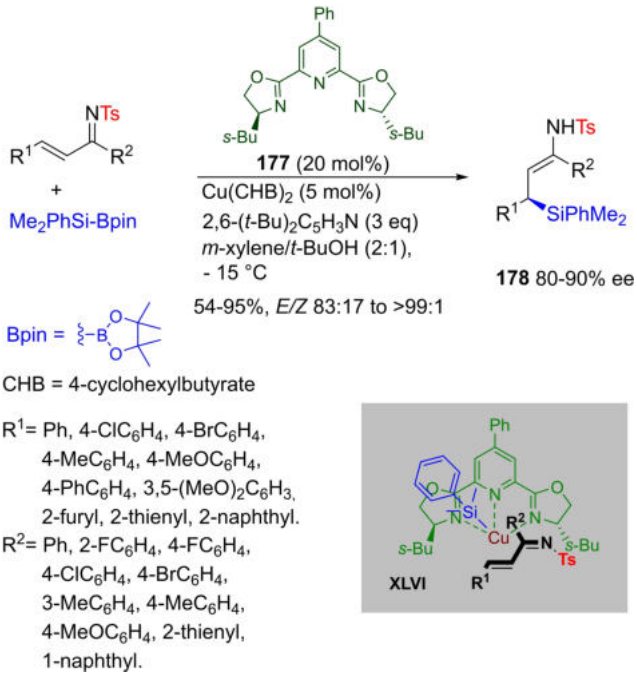
11. Reduction of *N*-Activated Ketimines

The enantioselective catalyzed reduction of activated ketimines represents a complementary approach to the addition of carbon nucleophiles to activated aldimines for the synthesis of α,α-disubstituted amino derivatives (Scheme 74).[116]

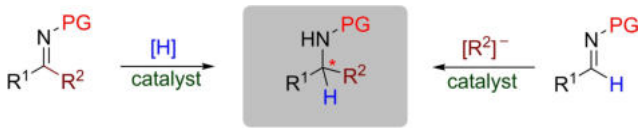
Different reducing agents coupled with various organometallic complex catalysts have been used for this purpose while organocatalyzed procedures are



Scheme 72. Asymmetric synthesis of *N,S*-acetals by addition of thiols to trifluoromethyl ketimines.



Scheme 73. Enantioselective conjugate protosilylation of α,β-unsaturated tosyl ketimines.

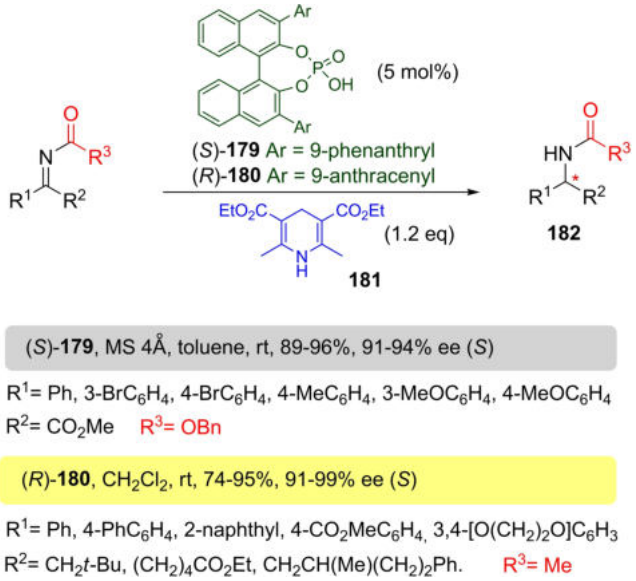


Scheme 74. Complementary synthetic strategies for the preparation of α,α-disubstituted amino derivatives.

poorly represented for this process. The utilization of hydrogen gas usually requires high pressures (30–75 atm) and only recently very efficient catalytic systems enable the reduction process to be carried out at normal pressure. Alternatively, transfer hydrogenations with alcohols (methanol, isopropanol) or formic acid and its salts can be used under mild reaction conditions. Finally, silanes can be profitably employed as reducing agents in the presence of several organometallic complexes.

11.1. Organocatalyzed Reductions

Currently, only a couple of similar organocatalyzed procedures is available for the reduction of activated ketimino esters using the Hantzsch ester **181** in the presence of chiral phosphoric acids (Scheme 75). The first procedure employs catalyst (*S*)-**179** and is effective on *N*-benzyloxycarbonylketimino esters.[15] Interestingly this method is selective for this *N*-carbamoyl group since the *N*-benzoylketimino analogues gave totally unsatisfactory results. The alternative process using (*R*)-**180** efficiently works on *N*-acetylarylalkylketmines bearing several functionalized alkyl moieties.[16]



Scheme 75. Enantioselective reduction of *N*-acylketimines by the Hantzsch ester catalyzed by chiral phosphoric acids.

11.2. Palladium-Catalyzed Reductions

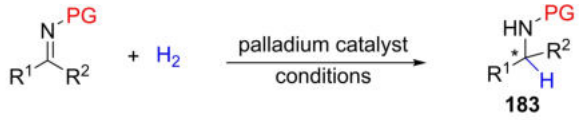
Palladium complexes with diphosphine chiral ligands are widely used in homogeneous catalytic reductions with molecular hydrogen.[117] The results of this process using activated imines as substrates are summarized in Table 2.[118–123] *N*-arylsulfonylketimines are the most employed substrates for the preparation of arylalkylamino derivatives **183**. Ketimino esters can also be profitably used to access α-amino carboxylic acid derivatives as well as their phosphorous analogues. For most of the catalysts employed the chemical yield and the enantioselectivity are only moderately affected by the nature of the substituents included in the aryl group. Conversely, the quinoxaline-derived phosphine ligand **190** is rather sensitive to the steric hindrance provided by the substrate aryl moiety since 2-substitued phenyl ketimino esters give modest results (59–88% ee) (Table 2, entry 7).[123] The same effect is probably responsible for the disappointing results observed using a *t*-butylketimino ester while related ketimines bearing a *t*-butyl group can be successfully reduced using the Pd-complex with ligand **186** (Table 2, entry 3).[119] The ketimines employed in this process are usually enough reactive toward the catalyst used but the reaction carried out with ligand **189** requires a further activation of the ketimine provided by zinc(II) triflate (Table 2, entry 6).[122] The hydrogen pressure applied in these reductive processes was initially rather high (41–75 atm) at variable temperatures but the last devised catalysts show superior performances allowing the reduction at 1 atm even at room temperature (Table 2, entries 6,7).

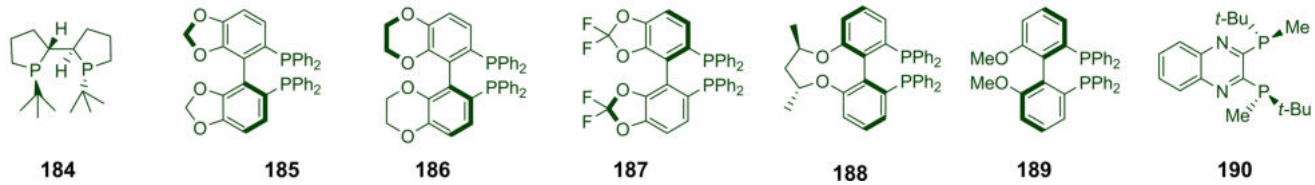
Reduction of *N*-phenylsulfonylketimines by palladium-catalyzed asymmetric transfer hydrogenation using methanol as hydrogen source has been recently reported (Scheme 76).[124] The chiral palladium-ligand **191** complex reacts with methanol leading to the monomethoxylated intermediate **XLVII** which by assistance of the zinc(II) cation generates the palladium hydride species **XLVIII**. The enantioselective reduction of the ketimine by the palladium hydride ultimately affords the target amino derivatives **192**. The mechanistic course of the process has been confirmed by deuterium-labelling experiments using CD_3OH.

11.3. Iron-Catalyzed Reductions

The complex obtained mixing iron carbonyl hydride cluster complex $[Et_3NH][HFe_3(CO)_{11}]$ with diphosphine ligand **193** is very effective in the transfer hydrogenation of *N*-diphenylphoshinoylketimines even at very low catalyst loading (Scheme 77).[125] The presence of a catalytic amount of base is essential for a fast process (0.5 h) and to obtain high values of enantioselectivity in the formation of amino derivatives

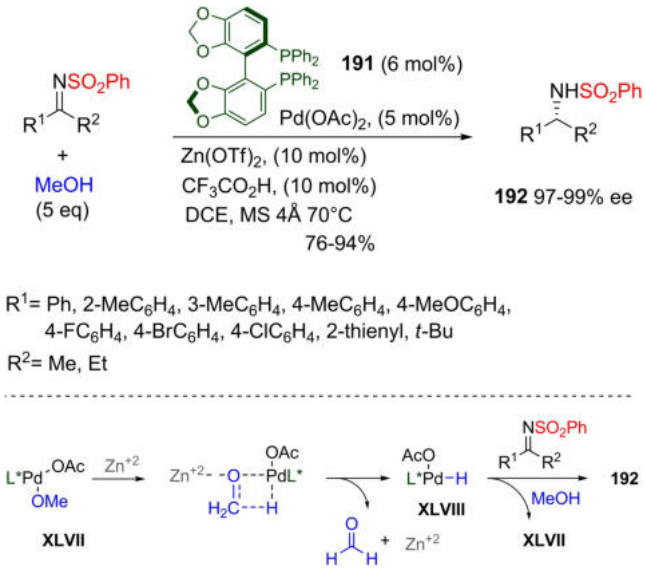
Table 2. Asymmetric organopalladium catalytic hydrogenation of *N*-activated ketimines.



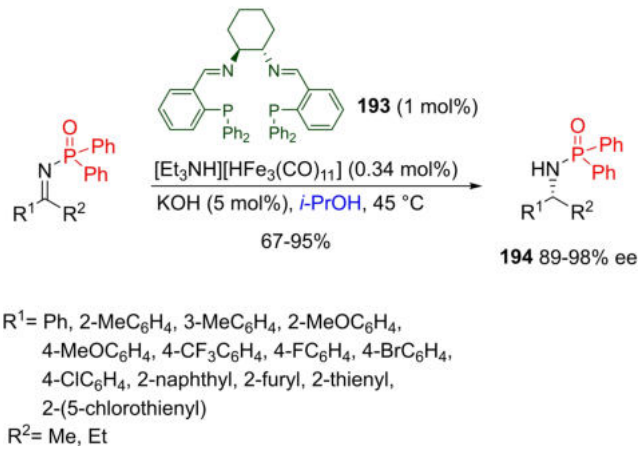


Entry	PG	R^1	R^2	Catalyst (mol%)	Conditions	Yield (%)	Ee (%) [abs.conf.]	Ref.
1	*p*-Tol SO_2	Aryl, *t*-Bu	Me, Et	**184** (1.2) $Pd(OCOCF_3)_2$ (1)	H_2 (75 atm), CH_2Cl_2, 40 °C	>99[a]	75–99 [*R*]	[118]
2	$Ph_2P{=}O$	Aryl	Me, Et	**185** (2.4) $Pd(OCOCF_3)_2$ (2)	H_2, (68 atm), TFE, rt	29–98	87–99 [*S*]	[119]
3	*p*-$TolSO_2$	Aryl, *t*-Bu	Me, Et	**186** (2.4) $Pd(OCOCF_3)_2$ (2)	H_2, (41 atm), TFE, rt	84–98	88–97 [*S*]	[119]
4	*p*-$TolSO_2$	Aryl	$(RO)_2P{=}O$	**187** (2.4) $Pd(OCOCF_3)_2$ (2)	H_2, (41 atm), TFE-CH_2Cl_2, (2:1), 40 °C	91–98	85–97 [*S*]	[120]
5	*p*-$TolSO_2$	Aryl	$(RO)_2P{=}O$	**188** (2.4) $Pd(OCOCF_3)_2$ (2)	H_2, (41 atm), TFE-CH_2Cl_2, (2:1), 40 °C	91–97	93–98 [*R*]	[121]
6	$ArSO_2$	Aryl	Me	**189** (6) $Pd(OAc)_2$ (5)[b]	H_2, (1 atm), DCE, 70 °C	35–94	75–99 [*R*]	[122]
7	*p*-$TolSO_2$	Aryl	CO_2R, $CONR_2$	**190**(2) $Pd(OAc)_2$ (2)	H_2, (1 atm), TFE, rt	92–97	59–97 [*R*]	[123]

[a] Conversion.
[b] $Zn(OTf)_2$ (10 mol%) is used as additive.



Scheme 76. Reduction of *N*-phenylsulfonyl ketimines by palladium-catalyzed asymmetric transfer hydrogenation.

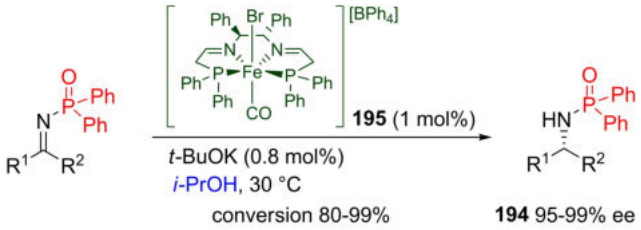


Scheme 77. Asymmetric transfer hydrogenation of *N*-diphenylphosphinoylketimines using an iron cluster complex and chiral diphosphine ligand **193**.

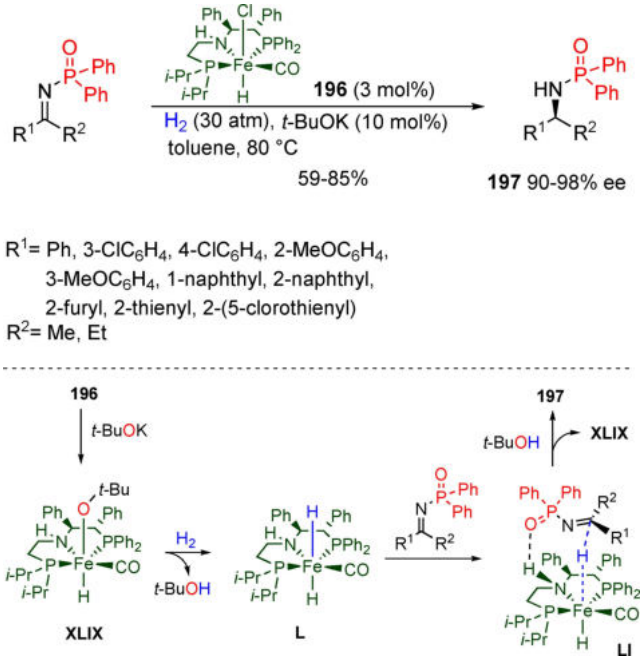
194. Dialkyl ketimines are poorly effective in this reaction in term of chemical yields and enantioselectivity. The chiral iron complex **195**, has been employed in the same reaction under milder reaction conditions

(Scheme 78).[126] The catalyst and the reaction conditions adopted in this reductive process are highly selective for *N*-diphenylphosphinoylketimines since *N*-arylsulfonyl and *N*-acyl ketimines do not give appreciable results.

The versatility of chiral iron complexes has been recently also demonstrated in the asymmetric hydrogenation using molecular hydrogen at moderate pressure (Scheme 79).[127] Reduction of *N*-diphenylphosphinoylketimines with iron catalyst **196** affords the corresponding amino derivatives **197** in satisfactory yields and excellent enantioselectivity except in the case of dialkylketimine substrates. Activation of the iron catalyst toward the hydrogen uptake is provided by potassium *t*-butoxide which substitutes the halogen atom leading to intermediate **XLIX**. The hydrogenated catalyst **L** reacts with the ketimine through the possible transition state **LI** in which hydrogen release occurs to the *Re* face of the substrate.



Scheme 78. Asymmetric transfer hydrogenation of *N*-diphenylphosphinoylketimines using an iron complex **195**.

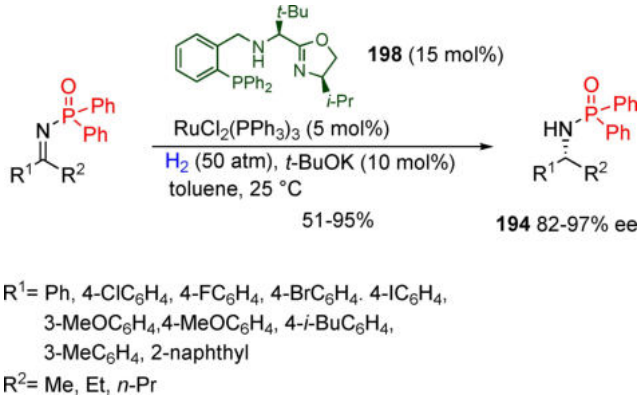


Scheme 79. Enantioselective catalytic hydrogenation of *N*-diphenylphosphinoylketimines by iron complex **196**.

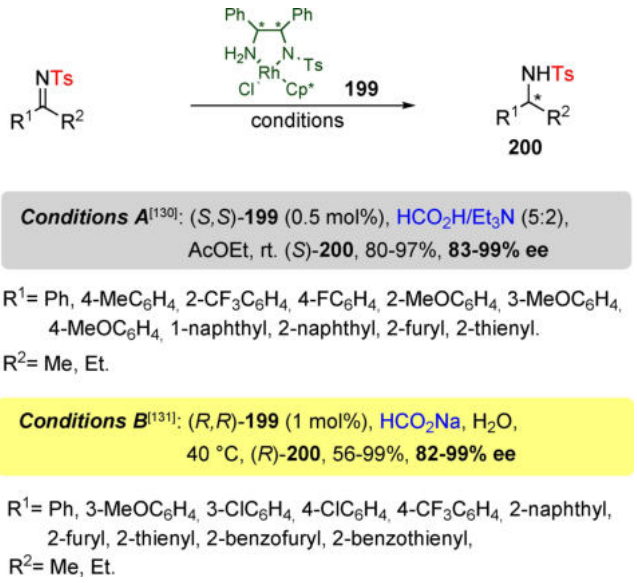
11.4. Ruthenium-, Rhodium-, Rhenium-, and Iridium-Catalyzed Reductions

Dendridic ligands embedding chiral 1,2-diamine moieties have been tested twenty years ago in the ruthenium-catalyzed asymmetric transfer hydrogenations of a single *N*-*t*-butylsulfonylketimine with modest results.[128] Recently, the ruthenium complex with chiral ligand **198** has been proposed for the hydrogenation of *N*-diphenylphosphinoylketimines (Scheme 80).[129] The active catalytic species is a dimeric ruthenium complex effective on a large number of substrates with the notable exception of diaryl and phenylcyclopropyl ketimines. The rhodium complex **199** based on the utilization of chiral diphenylethandiamine has been successfully employed in the asymmetric transfer hydrogenation of *N*-tosylketimines (Scheme 81). Both enantiomers of the complex **199** have been tested for the reduction although under different reaction conditions. The (*S,S*) enantiomer has been used in very reduced amount using a mixture of formic acid and triethylamine in ethyl acetate as solvent at room temperature.[130] Reductions with the (*R,R*) enantiomer have been carried out in water at 40 °C using sodium formate as hydrogen donor.[131] In the latter procedure a substantial improvement is observed for some examples adding a catalytic amount of the nonionic surfactant Triton X-100.

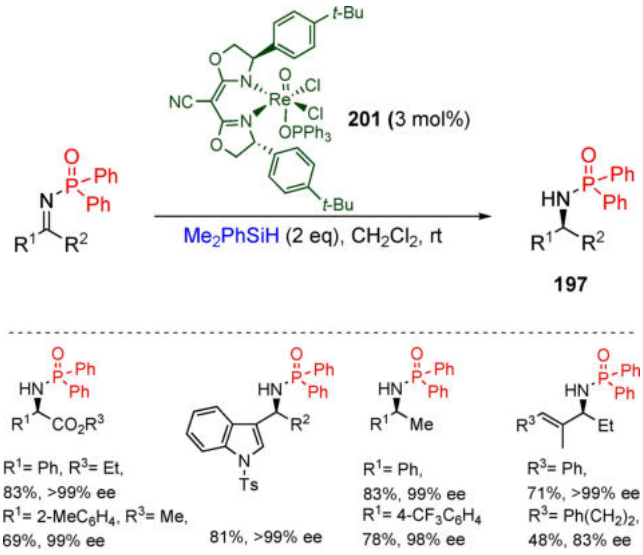
The enantioselective reduction of *N*-diphenyl-phosphinoylketimines has been successfully realized using phenyldimethylsilane in the presence of a chiral bisoxazoline oxorhenium complex **201** (Scheme 82).[132] The reaction is effective on a large



Scheme 80. Enantioselective catalytic hydrogenation of *N*-diphenylphosphinoylketimines by a ruthenium complex.



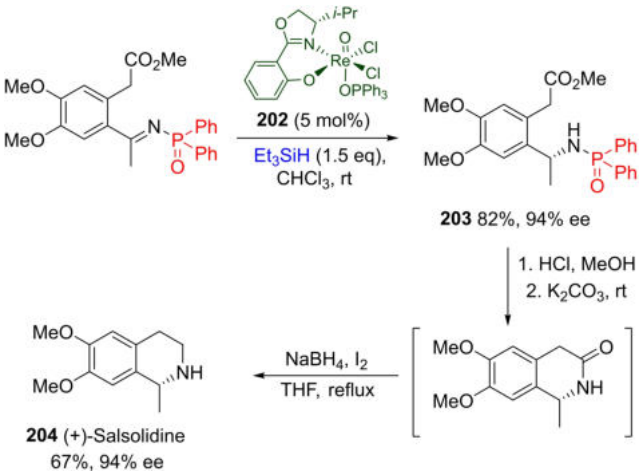
Scheme 81. Asymmetric transfer hydrogenation of *N*-tosylketimines using chiral rhodium complexes **199**.



Scheme 82. Reduction of *N*-diphenylphosphinoylketimines with phenyldimethylsilane catalyzed by chiral oxorhenium complex **201**.

variety of substrates including ketimino esters, and α,β-unsaturated ketimines. The latter substrates are reduced chemoselectively at the imino moiety leading to enantioenriched allylamino derivatives. As observed in previously discussed procedures, ketimines bearing dialkyl groups on the azomethine carbon give very low levels of enantioselectivity.

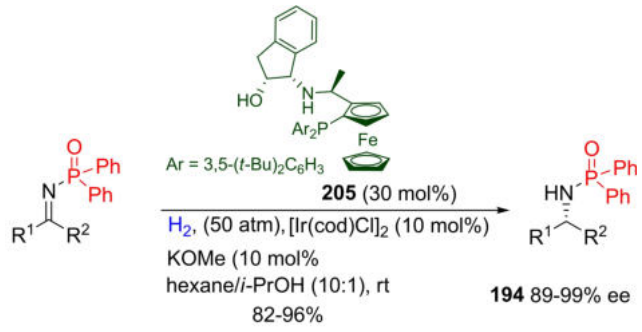
Later on, a related chiral salicyloxazoline oxorhenium complex **202** has been introduced for the reduction of the same substrates using triethylsilane (Scheme 83).[133] The level of efficiency and limits



Scheme 83. Enantioselective synthesis of (+)-salsolidine.

displayed by this catalyst parallel these observed with complex **200** and the usefulness of that procedure has been tested for the synthesis of the naturally occurring tetraisoquinoline (+)-salsolidine **204**. The *N*-diphenylphosphinoylamine **203** has been obtained in good yield and enantioselectivity from the corresponding ketimine. Removal of the phosphinoyl group under acidic conditions followed by basic treatment gave a chiral dihydroisoquinolinone which without purification was reduced to (+)-salsolidine **204**.

Catalytic hydrogenation of *N*-diphenylphosphinoylketimines can be also pursued using a chiral iridium catalyst obtained mixing *in situ* ferrocene-based tridentate ligand **205** and $[Ir(cod)Cl]_2$ (Scheme 84).[134] This is a high yielding process particularly suitable for the gram-scale reduction of arylalkyl ketimines but is



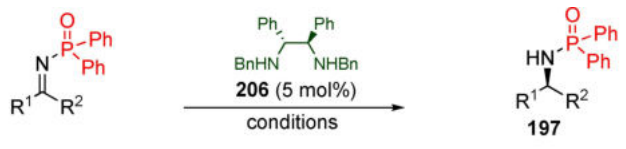
R1= Ph, 4-MeC6H4, 3-MeOC6H4, 4-MeOC6H4, 2-FC6H4,
3-FC6H4, 4-FC6H4, 4-ClC6H4, 4-BrC6H4, 4-CF3C6H4,
3,5-(CF3)2C6H3, 1-naphthyl, 2-naphthyl, 2-furyl, 2-thienyl
R2= Me, Et

Scheme 84. Catalytic hydrogenation of *N*-diphenylphosphinoylketimines using an iridium complex.

much less effective for dialkyl ketimines which give rather low conversions and enantioselectivities.

11.5. Zinc-, Copper-, and Nickel-Catalyzed Reductions

The metal complexes obtained combining zinc derivatives with chiral 1,2-diamines have been successfully used in the reduction of various activated ketimines with silane reagents. In the example displayed in Scheme 85, *N*-diphenylphosphinoyl ketimines are reduced to the corresponding amino derivatives **197** using zinc complexes with chiral diamine **206**. In the former procedure the metal complex was obtained using diethylzinc and as reducing agent was employed polymethylhydrosiloxane (PMHS).[135] Although tested on a limited number of substrates this method is highly



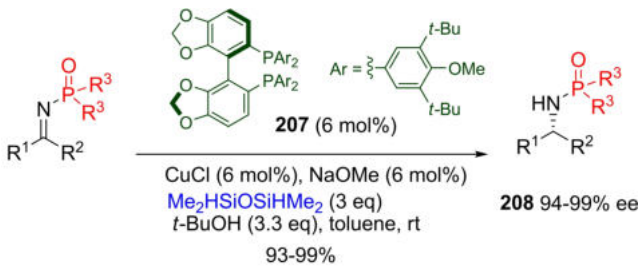
Conditions A[135]: Et_2Zn (5 mol%), PMHS (3 eq), THF/MeOH (4:1), rt, 74-86%, **96-97% ee**

R^1= Ph, 4-BrC_6H_4, 4-$MeOC_6H_4$, 2-furyl
R^2= Me, Et.

Conditions B[136]: $Zn(OAc)_2$ (5 mol%), $(EtO)_3SiH$ (2 eq), THF, rt, 52-97%, **84-97% ee**

R^1= Ph, 2-$MeOC_6H_4$, 3-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-MeC_6H_4, 3-BrC_6H_4, 4-BrC_6H_4, 2-ClC_6H_4, 4-ClC_6H_4, 4-IC_6H_4, 1-naphthyl, 2-naphthyl, 2-furyl
R^2= Me, Et.

Scheme 85. Enantioselective reduction of *N*-diphenylphosphinoylketimines with silanes catalyzed by chiral zinc complexes.



R^1= Ph, 4-BrC_6H_4, 4-$MeOC_6H_4$, 4-$CF_3C_6H_4$
R^2= Me, Et, *i-Pr*
R^3= 3,5-$Me_2C_6H_3$

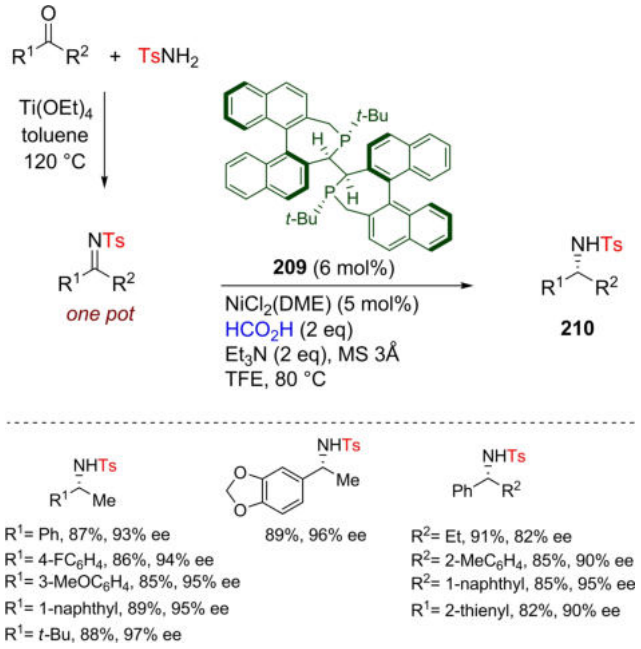
Scheme 86. Enantioselective reduction of *N*-diphenylphosphinoylketimines with silanes catalyzed by copper-ligand **207** complex.

effective except when a branched group is present in the ketimine (R^2 = *i*-Pr). Later on, a modified procedure was devised using the same ligand but zinc(II) acetate and triethoxysilane as reducing agent.[136] The utilization of PMHS is possible in this reaction but better yields are recorded using triethoxysilane as reductant. Zinc complexes using chiral cyclohexane-1,2-diamines have also been used in the reduction of *N*-diphenylphosphinoylketimines with PMHS and diphenylsilane but the effectiveness of the procedure has been evaluated only on a couple of substrates.[137,138]

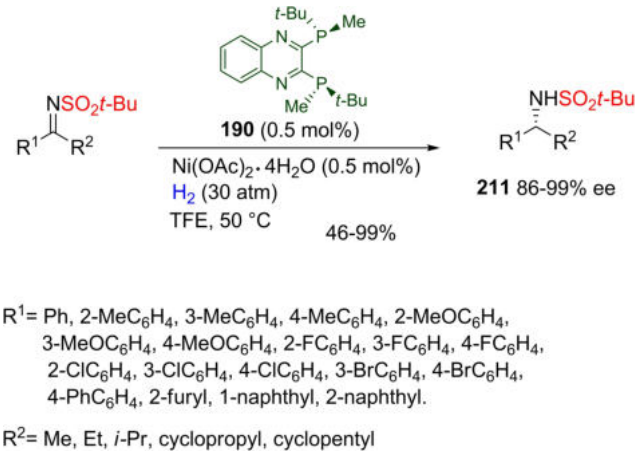
The hydrosilylation of *N*-dixylylphosphinoyl- ketimines has been pursued using a chiral complex obtained from copper(I) chloride and the diphosphine ligand **207** (Scheme 86).[139] The reaction of the copper complex with tetramethyldisiloxane is assumed to generate a copper hydride species which is responsible for the enantioselective reduction of the ketimine. The reduced products **208** are obtained in high yield and enantioselectivity. This asymmetric hydrosilylation has been realized using an heterogeneous catalyst prepared starting from the same chiral ligand and copper dispersed in charcoal.[140] Although the yields of the obtained amines **208** are superior compared to the homogeneous method, the recorded enantioselectivity for the same products is definitely lower.

The nickel-catalyzed processes for the reduction of activated ketimines have been introduced only very recently and are restricted to the utilization of *N*-sulfonylketimines. *N*-Tosylketimines prepared from the corresponding ketones as reported in Scheme 8 have been formerly used in a one pot process simply adding to the cooled mixture the (*S*)-Binapine ligand **209**, nickel(II) chloride and formic acid as hydrogen transfer reagent (Scheme 87).[141] The reaction is effective on a large array of substrates including diaryl and dialkyl ketimines which often give moderate levels of enantioselectivity in products **210** with other catalytic systems.

The nickel complex with ligand **209** has also been employed in the asymmetric transfer hydrogenation of *N*-arylsulfonylketimines using isopropanol as reductant.[142] The enantioselectivity obtained under these conditions is similar to that recorded in the one-pot procedure and the utilization of isopropanol-d_8 allows the efficient preparation of α-deuterated amino derivatives **210**. High pressure hydrogenation of *N*-*t*-butylsulfonylketimines in the presence of the nickel complex with chiral quinoxaline-diphosphine **190** affords the amino derivatives **211** with excellent enantioseletivity (Scheme 88).[143] The process is featured by a reduced catalyst loading (0.5 mol%) which for large scale operations can be further lowered to 0.033 mol%. The utilization of deuterium gas allows the preparation of α-deuterated sulfonylamines **211** suggesting a catalytic mechanism similar to that observed for palladium-catalyzed reactions. A chemo

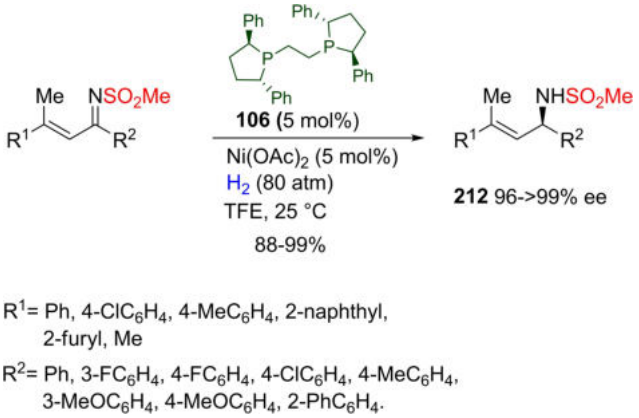


Scheme 87. Asymmetric synthesis of *N*-tosylamines **210** by a one-pot process from ketones.



Scheme 88. Enantioselective catalytic hydrogenation of *N*-tosylketimines using a nickel-chiral diphosphine complex.

and enantioselective catalytic hydrogenation of β-disubstituted α,β-unsaturated *N*-mesylsulfonyl-ketimines can be carried out using a chiral Ni-diphospholane **106** complex (Scheme 89).[144] The corresponding allylamino derivatives **212** are obtained in good yields and excellent enantioselectivity. The utilization of the chalcone-derived *N*-mesylketimine also gives a good result in the enantioselective reduction (ee 96%) but in reduced yield (60%).



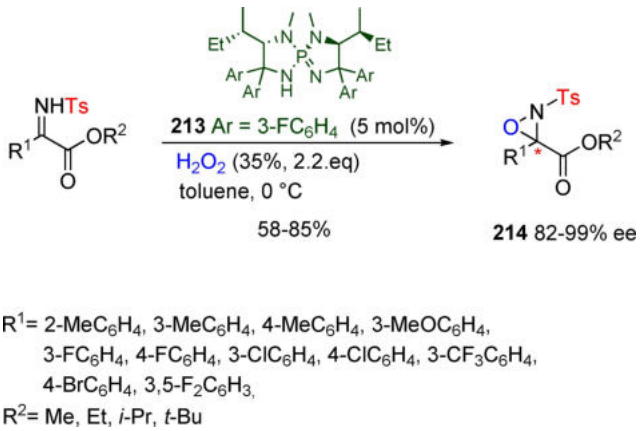
Scheme 89. Regioselective asymmetric hydrogenation of α,β-unsaturated ketimines by a chiral nickel-diphospholane complex.

12. Epoxidation

Optically active oxaziridines can be prepared by epoxidation of *N*-tosylketimino esters with aqueous hydrogen peroxide in the presence of chiral triaminoiminophosphorane **213** (Scheme 90).[145] Although the absolute configuration of the resulting oxaziridines **214** has not been determined, these products are generally obtained in good yield and enantioselectivity. The application of these chiral oxaziridines has been evaluated for the oxidative conversion of silyl enol ethers into the corresponding optically active 2-hydroxy ketones with satisfactory results.

13. Conclusions and Outlook

The development of improved protocols for the asymmetric synthesis of amino derivatives through the addition of nucleophiles to azomethine systems has



Scheme 90. Asymmetric epoxidation of ketimino esters by hydrogen peroxide in the presence of phosphorane **213**.

been largely focused on the utilization of aldimino derivatives as electrophilic substrates. The reduced reactivity of unactivated ketimines which parallels that of ketones compared to aldehydes has often limited their inclusion in synthetic plans aimed at the preparation of amino-containing compounds. However, a significant increase in the electrophilic character of ketimines can be achieved introducing electron-withdrawing acyl, carbamoyl, sulfonyl and phosphinoyl groups on the nitrogen atom. The enantioselective catalyzed nucleophilic addition on these azomethine substrates generally occurs under mild and controlled conditions giving α-trisubstituted primary amino derivatives conveniently protected at the nitrogen atom. A notable number of nucleophilic reagents including organometallics, stabilized carbanions, electron-rich aromatic derivatives and heteronucleophiles can be used in the reaction with *N*-activated ketimines. Besides, asymmetric reduction of the carbon-nitrogen double bond under homogeneous catalyzed conditions represents a complementary approach to the synthesis of α-disubstituted amino derivatives otherwise obtainable by nucleophilic addition to aldimines. Similarly to enone derivatives, α,β-unsaturated *N*-activated ketimines mainly undergo to conjugate additions in the reaction with nucleophiles. The resulting enamides can be isolated as final products or more frequently involved in cascade processes leading to the formation of nitrogenated heterocyclic compounds. These unsaturated ketimines can also be involved as heterodienes in inverse-electron-demand aza-Diels-Alder processes for the synthesis of related heterocyclic compounds. The steric crowding around the reaction center in *N*-activated ketimines still causes some limitation in the nature of nucleophiles usable for the addition reaction. Nitroalkanes other than nitromethane as well as α,α-disubstituted enolates are unusable for this process. More than half of the papers discussed in this article have been appeared in literature during the last five years and this testify the growing interest in the chemistry of *N*-activated ketimines. Despite this, the practical utilization of these procedures to the asymmetric synthesis of specific target compounds is still largely underdeveloped. In this context, the content of this review article is also aimed at encouraging the use of *N*-activated ketimines in the stereoselective synthesis of targeted amino derivatives.

Acknowledgements

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