



Transition metal-catalyzed reactions of *N*-sulfinyl imines

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ABSTRACT

Transition metal-catalyzed reactions of *N*-sulfinyl imines with several substrates lead to the corresponding chiral amines with high yields and diastereo- or enantioselectivities. As metals, titanium, copper, ruthenium, rhodium, palladium and silver have been successfully used as catalysts in different carbon-carbon forming reactions as well as hydrogenations with molecular hydrogen or transfer hydrogenations with isopropanol as hydrogen source.

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Introduction

Chiral *N*-sulfinyl imines are important starting materials in asymmetric synthesis because in the reaction with carbon nucleophiles a new carbon-carbon bond is formed and a new stereocenter is generated [1]. As nucleophiles mainly organometallic reagents have been used, such as organoalkaline, organomagnesium, organozinc, organoboron, organoaluminium, organoindium and organosilicon compounds [2]. In our group we have been investigating the indium-promoted allylation of chiral *N*-sulfinyl imines [3] and its application to the synthesis of several chiral nitrogen-containing compounds, especially natural alkaloid derivatives [4]. Since the starting chiral imines are easily accessible in pure enantiomeric form from commercially available materials [5], this methodology has been used successfully for the enantio- [6a] and diastereoselective [6b] allylation of imines [7,8]. In this account we will consider non-exhaustively the transition metal-catalyzed reaction of *N*-sulfinyl imines with different substrates in order to get nitrogen-containing compounds in an enantioselective manner.

Titanium

Titanium tetraisopropoxide catalyzed the addition of the anion derived from oxindoles **2** to α -fluorinated imines **1** in THF at low temperature. Thus, the corresponding products **3** were obtained in good to excellent yields and almost total diastereo- and enan-

tioselectivities (Scheme 1) [9]. The observed stereochemistry could be explained considering the participation of intermediate **I** in the process. Deprotection of one compound **3** (AcCl, *i*PrOH-EtOH, 0 °C) allowed the preparation of the corresponding amine in high yield (97%).

The same starting materials **1** reacted with the lithium reagent derived from 2-alkylpyridines **4** in the presence of titanium tetraisopropoxide to yield the expected compounds **5** with modest to good yields and high diastereoselectivities (Scheme 2) [10]. Intermediate **II** has been postulated in order to explain the obtained results. Also in this case one of the products **5** was deprotected (MeOH, dioxane, HCl) to afford the corresponding primary amine with excellent yield (98%).

Butenolides **6** react with sulfonamide **7** in the presence of titanium tetraethoxide to give, after reduction with L-Selectride at low temperature, the corresponding protected amino esters **8** (Scheme 3) [11]. Orthogonal deprotection of compounds **8** afforded the expected products in excellent yields. Non-isolated imines **III** were proposed to be formed and *in situ* reduced to the final products, and intermediate **IV** seems to be involved in the process.

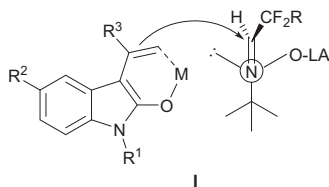
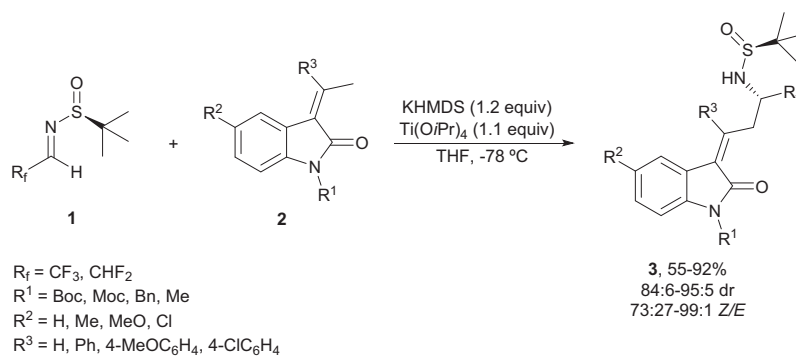
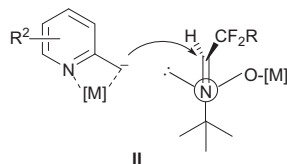
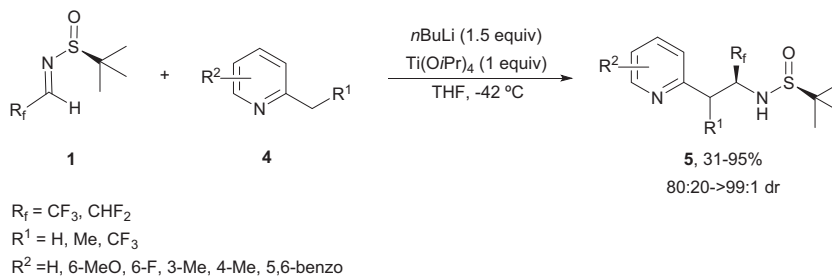
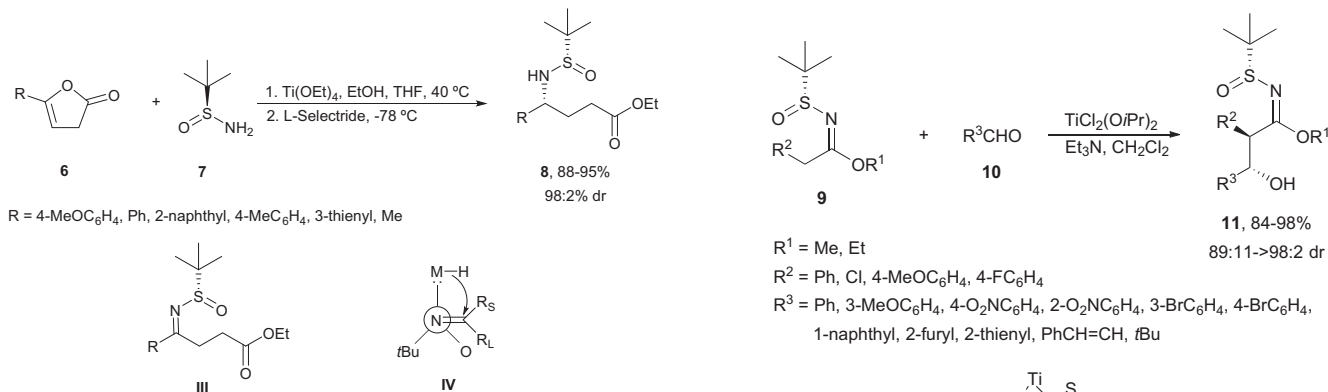
Finally, sulfinyl imidates **9** reacted with aldehydes **10** in the presence of TiCl₂(*Oi*Pr)₂ to yield mainly the corresponding *anti*-products **11** with both high yields and diastereoselectivities (Scheme 4) [12]. The favored transition state **V** has been postulated to explain the observed stereochemistry in this aldol-type process.

Copper

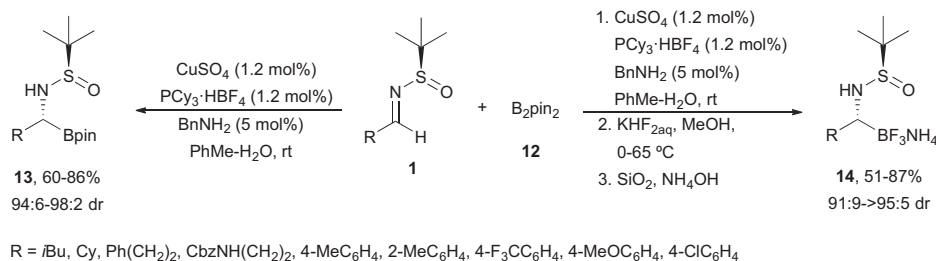
Imines **1** react with bis(pinacolato)diboron **12** in the presence of CuSO₄ and PCy₃-HBf₄ to give the corresponding products **13** with

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Scheme 1. Preparation of compounds **3** from imines **1** and oxindoles **2**.Scheme 2. Preparation of compounds **5** from **1** and **4**.Scheme 3. Preparation of compounds **8** from **6** and **7**, followed by reduction.Scheme 4. Preparation of compounds **11** from **9** and **10**.

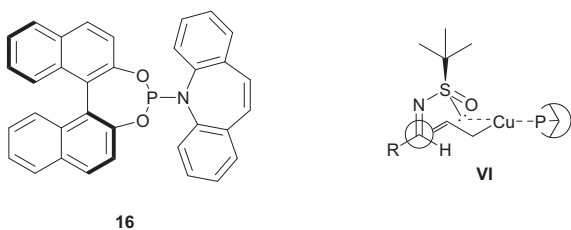
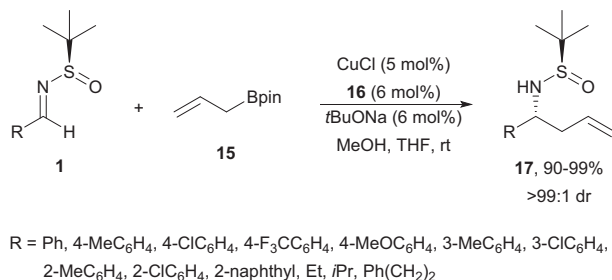
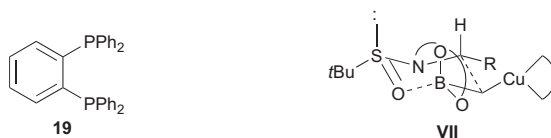
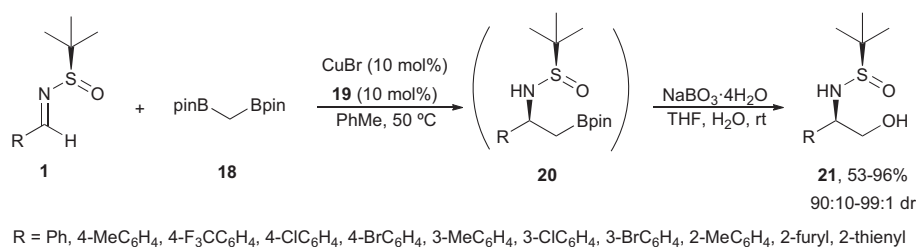
good yields and excellent diastereoselectivities (Scheme 5) [13]. When products **13** were *in situ* successively treated with KHF_2 and $\text{SiO}_2\text{-NH}_4\text{OH}$ the expected tetrahydroborates **14** were the reac-

Scheme 5. Preparation of compounds **13** and **14** from **1** and **12**.

tion products obtained also with good yields and excellent diastereoselectivities. These processes were also applied to a couple of ketimines with similar results.

The CuCl-catalyzed allylation of imines **1** with the allylborane **15** in the presence of the chiral ligand **16** led to the formation of protected homoallyl amine **17** with excellent yield and diastereoselectivity (Scheme 6) [14]. The observed stereochemistry was explained considering the transition state **VI**. On the other hand, the process was also applied to ketimines derived from acetophenones with similar results.

When imines **1** were allowed to react with the diborylmethane **18** under CuBr catalysis and in the presence of phosphine **19** the

Scheme 6. Preparation of compounds **17** from **1** and **15**.Scheme 7. Preparation of compounds **21** from **1** and **18** and further oxidation.

corresponding products **20** were obtained, which were oxidized *in situ* with sodium borate to yield finally protected aminoalcohols **21** (Scheme 7) [15]. Transition state **VII** can explain the stereochemistry observed in the reaction.

Ruthenium

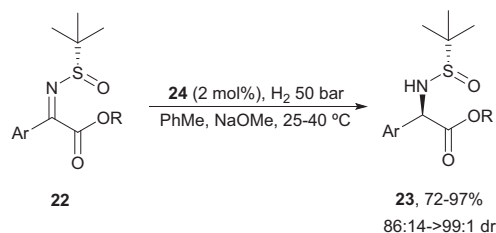
The Ru-catalyzed hydrogenation of several α -imino esters **22** led mainly to the formation of α -amino esters **23** (Scheme 8) [16]. As the Ru catalyst Ru-MACHO (**24**) was efficiently used and the corresponding products **23** were isolated in both excellent yields and diastereoselectivities.

The Ru-catalyzed transfer hydrogenation of ketimines **25** using isopropanol as hydrogen source and an amino alcohol as ligand under basic conditions afforded the corresponding chiral sulfinyl amines which were *in situ* deprotected to the corresponding primary amines **26** [17]. As amino alcohol, initially the indanol derivative **27** was the most efficient as shown in Scheme 9 [18].

An interesting simplification of the above mentioned protocol was the use of the achiral amino alcohol 2-amino-1,1-dimethylethanol as ligand. Under the same reaction conditions, the same amines **26** were obtained with similar results (Scheme 10) [19].

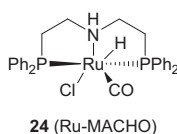
It is remarkable to underline that the methodology shown in Scheme 10 gives excellent results for aliphatic amines, compared to the procedure described in Scheme 9. Mechanistic calculations (DFT) showed that the reaction involves two transition states and three intermediates, so being a step-wise process and not a concerted one [20]. When the starting material with the opposite configuration was used, the corresponding enantiomeric primary amine was isolated.

A further improvement of the methodology shown in Scheme 10 was the use of microwaves (40 W) instead of heating: yields and enantioselectivities are similar but the reaction times are significantly reduced (from 1 to 4 h to less than 30 min) [21].

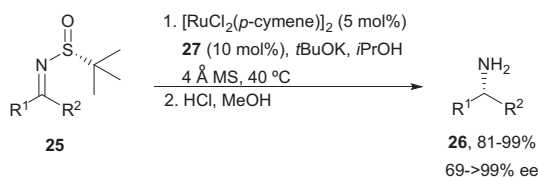


Ar = Ph, 2-MeC₆H₄, 3-MeC₆H₄, 4-MeC₆H₄, 2-MeOC₆H₄, 3-MeOC₆H₄,
4-MeOC₆H₄, 2-FC₆H₄, 4-FC₆H₄, 3-ClC₆H₄, 4-ClC₆H₄, 3-BrC₆H₄,
4-BrC₆H₄, 3,5-Me₂C₆H₃, 2,4-Me₂C₆H₃, 3,4-(OCH₂O)C₆H₃,
2-naphthyl, 9-phenanthryl

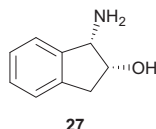
R = Me, Et, *i*Pr



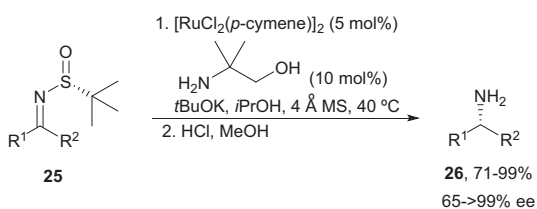
Scheme 8. Preparation of compound **23** from **22**.



R¹ = Cy, Ph, 4-BocNHC₆H₄, 3-MeOC₆H₄, 3-ClC₆H₄, 4-ClC₆H₄,
4-F₃CC₆H₄, 4-O₂NC₆H₄, 2-naphthyl, 2-furyl, 2-thienyl
R² = Me, Et, *n*Pr, CH₂Cl, (*E*)-PhCH=CH



Scheme 9. Preparation of amines **26** from imines **25**.



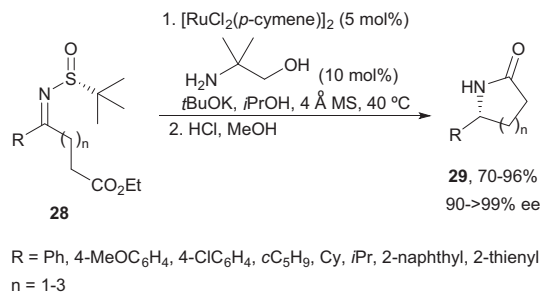
R¹ = Ph, 2-MeC₆H₄, 2-MeOC₆H₄, 4-BocNHC₆H₄, 3-MeOC₆H₄, 2-ClC₆H₄,
3-ClC₆H₄, 4-ClC₆H₄, 4-F₃CC₆H₄, 4-O₂NC₆H₄, 1-naphthyl, 2-naphthyl,
2-furyl, 2-thienyl, Ph(CH₂)₂, *i*Pr, Cy, *t*Bu

R² = Me, Et, *n*Pr, *i*Pr, Cy, (*E*)-PhCH=CH

Scheme 10. Preparation of amines **26** from imines **25**.

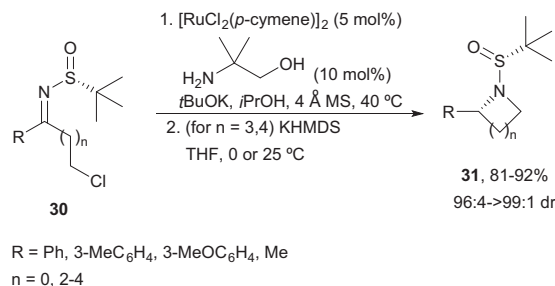
When the starting imine bears an ester group in one of the ω-positions, such as in **28**, a chiral amino ester was formed that after deprotection spontaneously cyclized to provide enantioenriched substituted lactams **29** (Scheme 11) [22]. In this case, both series of enantiomers were prepared.

The use of ω-chloro imines **30** allowed the preparation of *N*-sulfinyl nitrogen-containing heterocycles **31** (Scheme 12) [23]. In this case it was not possible to prepare the starting material with *n* = 1, because a β-elimination occurred under the reaction conditions assayed. For *n* = 0, 2–4 the reaction conditions depend on the struc-



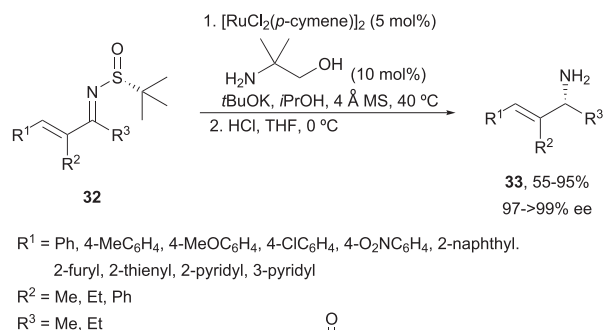
R = Ph, 4-MeOC₆H₄, 4-ClC₆H₄, cC₅H₉, Cy, *i*Pr, 2-naphthyl, 2-thienyl
n = 1-3

Scheme 11. Preparation of compounds **29** from **28**.

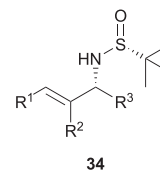


R = Ph, 3-MeC₆H₄, 3-MeOC₆H₄, Me
n = 0, 2-4

Scheme 12. Preparation of compounds **31** from **30**.



R¹ = Ph, 4-MeC₆H₄, 4-MeOC₆H₄, 4-ClC₆H₄, 4-O₂NC₆H₄, 2-naphthyl,
2-furyl, 2-thienyl, 2-pyridyl, 3-pyridyl
R² = Me, Et, Ph
R³ = Me, Et



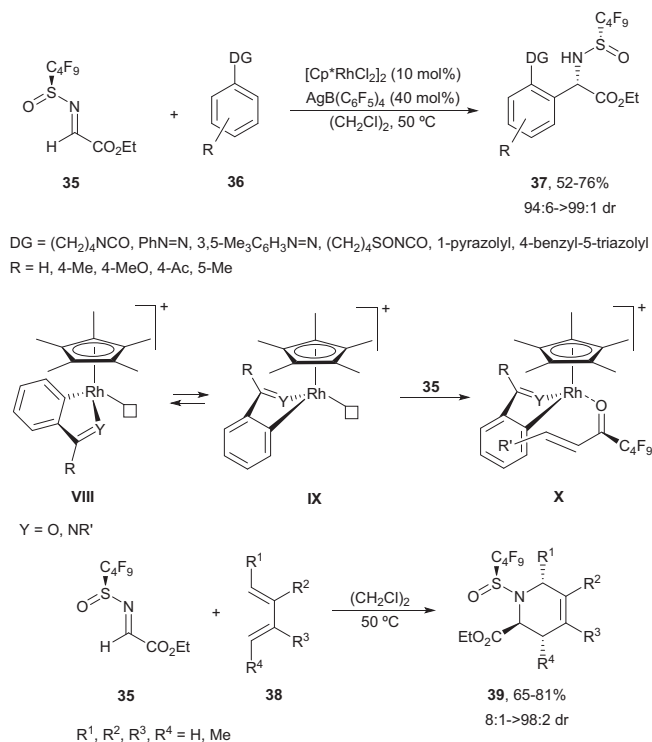
Scheme 13. Preparation of amines **33** from **32**.

ture of the reaction products: for aziridines and pyrrolidines (*n* = 0, 2) the basic conditions medium is sufficient for getting the cyclization. However, for *n* = 3, 4 an additional treatment with KHMDS was necessary to promote the cyclization, which in the case of *n* = 4 only worked using the corresponding ω-bromo derivative, instead the chloride.

The same reaction conditions used above have been applied to the synthesis of allyl amines **33** from α,β-unsaturated imines **32** (Scheme 13) [24]. In the case of *in situ* desulfonylation of **34** the corresponding primary amines were obtained with good yields and excellent enantioselectivities.

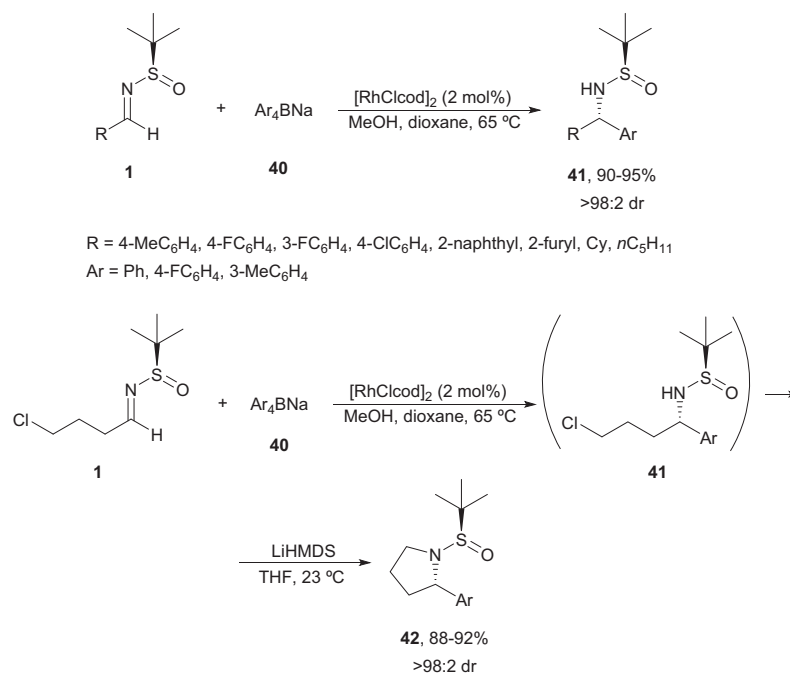
Rhodium

When perfluorobutane sulfinamide **35** reacted with differently substituted aromatic compounds bearing an *ortho*-directing group **36** in the presence of a catalytic amount of [Cp*RhCl₂]₂ and AgB (C₆F₅)₄, the corresponding products **37** were obtained with good



Scheme 14. Preparation of compounds **37** and **39** from **35** and **36** or **38**, respectively.

yields and excellent diastereoselectivities (**Scheme 14**) [25]. A mechanistic study involving intermediates **VIII-X** has been proposed to explain the obtained stereochemistry. In addition, compounds **35** was assayed as dienophiles in aza-Diels-Alder reactions with different substituted dienes **38**, so the corresponding products **39** were isolated with good yields and high stereoselectivities.



Scheme 15. Preparation of compounds **41** and **42** from imines **1** and sodium tetraarylborate **40**.

The Rh-catalyzed reaction of several imines **1** with sodium tetrafluoroborates **40** yielded the expected protected amines **41** with both excellent yields and diastereoselectivities (**Scheme 15**) [26]. When the starting imine **1** contains a chlorine atom at the ω -position the same reaction, followed by *in situ* treatment with LiHMDS afforded the corresponding pyrrolidines **42** with similar results.

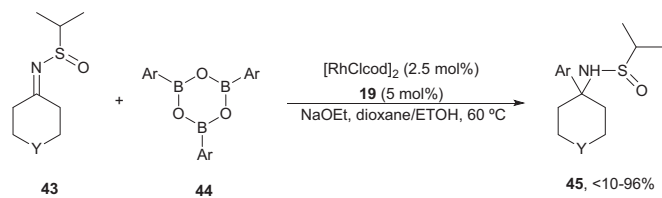
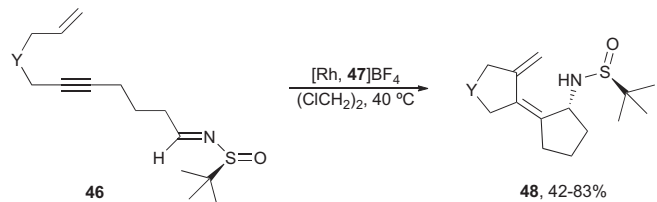
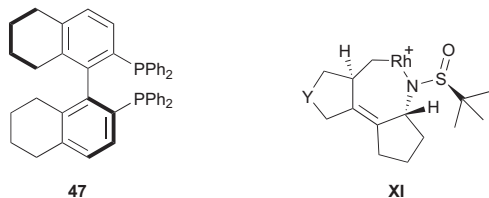
In the case of imines **43** derived from cyclic ketones, their Rh-catalyzed reaction with arylboroxine **44** in the presence of diphosphine **19** led to the corresponding arylated compounds **45** (**Scheme 16**) [27].

An intramolecular cyclization occurred when compound **46** were treated with a Rh-catalyst derived from (*S*)-H₈-BINAP (**47**) giving the corresponding product **48** as the only reaction adduct (**Scheme 17**) [28]. Intermediate **XI** has been proposed in order to explain the obtained stereochemistry. On the other hand, compounds **48** were assayed as dienes in Diels-Alder reactions with different dienophiles to afford the expected tricycles with excellent yields.

Palladium

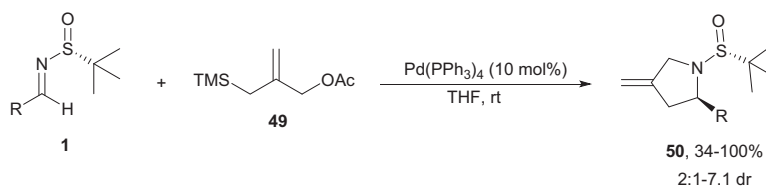
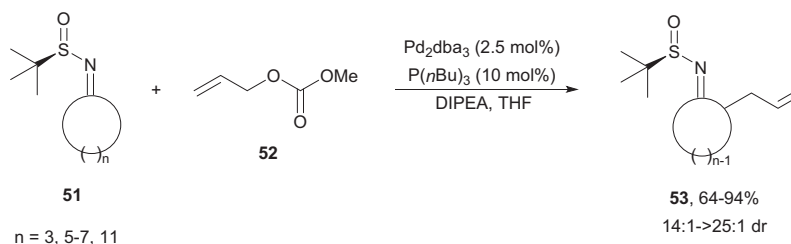
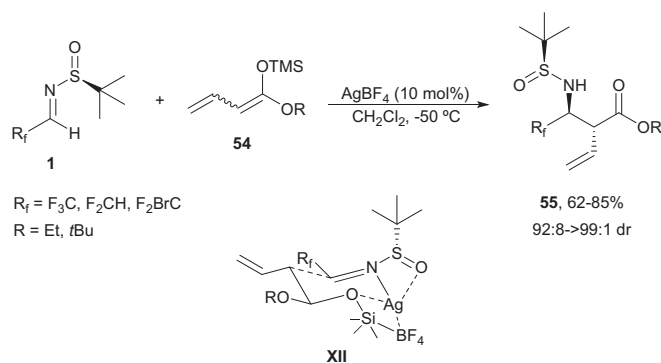
The reaction of several imines **1** with the precursor of trimethylenemethane **49** in the presence of a catalytic amount of Pd(PPh₃)₄ led to the formation of protected methylenide pyrrolidines **50** with good yields and diastereoselectivities (**Scheme 18**) [29]. The reaction was also extended to ketimines, which under the same reaction conditions afforded the corresponding heterocycles with both low yields and diastereoselectivities.

In the case of imines derived from cyclic ketones **51**, their allylation with allyl carbonate **52** in the presence of Pd₂dba₃ and P(*n*Bu)₃ allowed the formation of the corresponding α -monoallylated compounds **53** with high yields and diastereoselectivities (**Scheme 19**) [30]. The same reactions with methallyl or 3-phenylallyl carbonate afforded the corresponding products with similar results.

Y = CH₂, O, NBocAr = Ph, 4-MeOC₆H₄, 3-MeOC₆H₄, 4-MeC₆H₄, 3-MeC₆H₄, 2-MeC₆H₄, 4-FC₆H₄, 4-ClC₆H₄, 3-ClC₆H₄, 4-BrC₆H₄, 4-F₃CC₆H₄, 4-HOCH₂C₆H₄, 4-AcOC₆H₄, 3-AcC₆H₄**Scheme 16.** Preparation of compounds **45** from **43** and **44**.Y = (BnOCH₂)₂C, (AcOCH₂)₂C, Me₂C(OCH₂)₂C, 9-fluorenylidene, TsN, NsN**Scheme 17.** Preparation of compounds **48** from enynes **46**.

Silver

Silyl dienolates **54** react with imines **1** in the presence of AgBF₄ as catalyst to yield homoallyl amines **55** with excellent yields and diastereoselectivities (Scheme 20) [31]. Curiously, changing the silver salt by TMSOTf the structure of the final products changed

R = Ph, 4-MeOC₆H₄, 4-O₂NC₆H₄, 2-HOC₆H₄, 2-ClC₆H₄, 2-BrC₆H₄, Cy, tBu, 2-furyl, 2-thienyl, 2-naphthyl**Scheme 18.** Preparation of compounds **50** from **1** and **49**.**Scheme 19.** Preparation of compounds **53** from **51** and **52**.**Scheme 20.** Preparation of compounds **55** from **1** and **54**.

dramatically yielding δ-amino esters. A chelated transition state **XII** has been postulated to take part in the silver-catalyzed reaction in order to explain the obtained results.

Conclusions

From the results contained in this account we conclude that transition metal-catalyzed reactions of chiral aldimines and ketimines with different substrates represent a new way to prepare chiral amine derivatives, this methodology being complementary to that one using organometallic compounds derived from main group metals. Titanium, copper, ruthenium, rhodium, palladium and silver have been successfully used to catalyze several processes involving the addition to the C=N bond or the reaction at the α-position with respect to this bond. Some synthetic applications of these methodologies have been included in this short review.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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