Michael additions catalyzed by transition metals and lanthanide species. A review

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Dedicated to Professors José Elguero (CSIC-Madrid) and Pedro Molina (University of Murcia) on the occasion of their 70th and 60th anniversaries, respectively

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Abstract

Recent developments (1998–2004) in the transition-metal- and lanthanide- catalyzed Michael additions are analyzed. Their scope, limitations, induction of enantioselectivity, and mechanistic features are discussed.

Keywords: Conjugate addition, Michael addition, transition metal, lanthanide, catalysis

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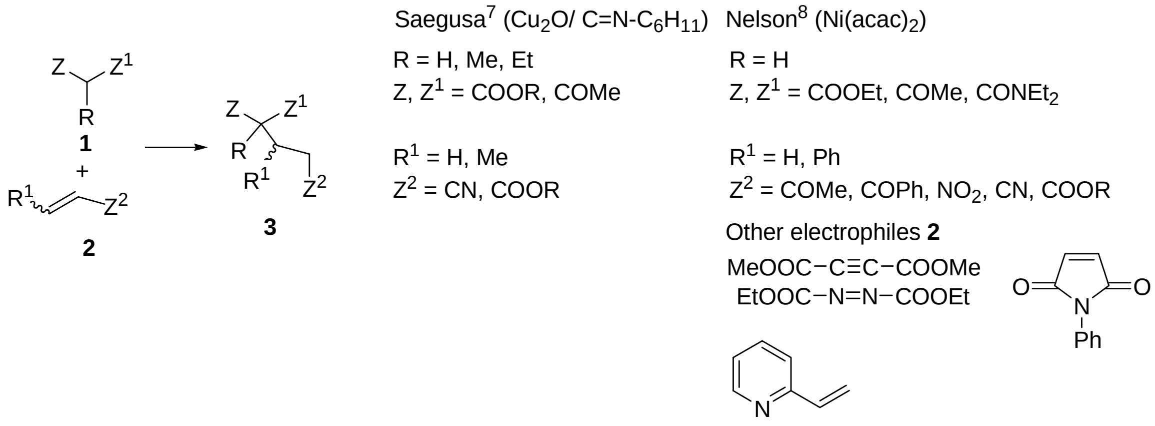
1. Introduction

The Michael addition of active methylene (and methine) compounds to activated π-systems is one of the oldest and more useful carbon–carbon bond-forming reactions (Scheme 1).[1,2] However, the required basic catalysis generates by-products arising from competing side reactions. Therefore, catalysis by transition metals or lanthanides, which work formally under neutral conditions, has attracted the attention of the chemical community. This is witnessed by the publication of many papers and a limited number of reviews. The most general review by Christoffers was published in 1998.[3] More specific reviews published by the same author,[4a,b] deal with the enantioselective construction of quaternary stereocenters, and still another review by Krause summarizes catalytic enantioselective Michael additions.[4c] We present here a general review embracing all progress —synthetic, mechanistic, and stereochemical— reported since 1998. We intend to update Christoffers' work concerning transition metals and lanthanides as catalysts. Only compounds featuring activated C-H bonds will be considered here. This includes β-diketones, β-ketoesters, malonates, cyanoacetates and the like, of type **1** (Scheme 1). Conjugate additions of ketone- and ester- silyl enol ethers and related compounds are not covered. Thus, the Mukaiyama–Michael reaction is not dealt with here. Furthermore, only transition metals and lanthanides acting in non-alkaline media are covered. This leaves out part of the enormous contribution by Shibasaki and others on BINOL hetero-bimetallic complexes featuring an alkaline alkoxide.[5] However, excellent reviews by Shibasaki's group are available, covering the enantioselective addition of malonates to cyclic unsaturated ketones.[5] A review on the induction of enantioselectivity in Michael additions has been published.[6] It covers both organocatalysis as well as catalysis by metal species.

In the present paper the values of the enantiomeric excess, *ee*, given in the Tables, are maximum values encountered in the relevant papers. Several terms frequently encountered in this article are formulated in Scheme 1.

Saegusa *et al*. in 1972 described the first Michael addition catalyzed by copper species.[7] Thus, the combination of copper(I) oxide and cyclohexyl isocyanide catalyzes the Michael additions shown in Scheme 1. The Saegusa reaction is quite general, both for nucleophiles and for electrophiles. Mechanistically the reaction may involve a copper-carbene species, although this has never been demonstrated.

Another important historical precedent is the Michael reaction catalyzed by nickel acetylacetonate [Ni(acac)$_2$] described by Nelson *et al.* in 1979–1980.[8] These workers reported on the Michael reactions of several non-substituted (**1**, R = H) β-dicarbonyl compounds with a broad variety of electrophiles (Scheme 1).



RCOCHRCOR	diketone
RCOCHRCOOR	ketoester
ROCOCHRCOOR	malonate
$NCCH_2COOR$	cyanoacetate
NCCHMeCOOR	cyanopropionate
O_2NCH_2COOR	nitroacetate
$NCCH_2SO_2R$	cyanosulfone

CH_2=$CHCOCH_3$	methyl vinyl ketone (MVK)
CH_2=CHCOR	vinyl ketone
ROCO-N=N-COOR	dialkyl azodicarboxylate
PhCH=CHCOPh	chalcone

Scheme 1. General Michael addition. Early results by Saegusa[7] and Nelson.[8]

The available information will be commented upon, according to the metal used, with special emphasis on the induction of enantioselectivity, both at the nucleophile and at the electrophile. However, it should be remembered that even when generating quaternary stereocenters, the stereochemical identity of the new stereogenic center could be compromised because the Michael addition is an essentially reversible reaction, and therefore a mechanism for racemization is always available.[9]

2. Michael addition catalyzed by transition metal species

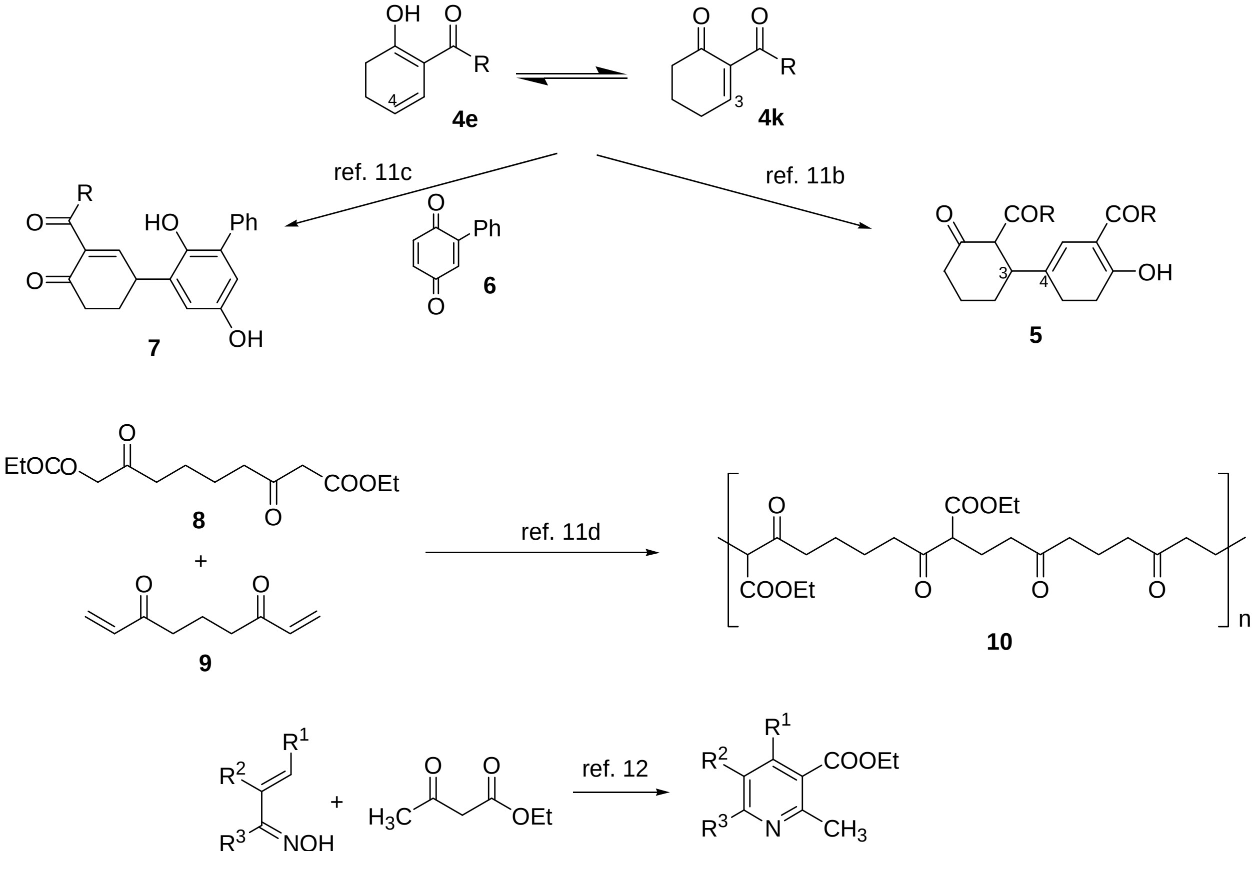
2.1 Group VIII. Iron (Table 1)

A general review on the use of iron compounds as catalysts in organic chemistry, has been published recently.[10] This paper includes Michael additions.

Iron- species have been used extensively by Christoffers as catalysts in the Michael addition. The review by this author contains all pertinent information prior to 1998.[3] Further developments by this group are based on the use of hydrated iron(III) chloride ($FeCl_3.6H_2O$): (i) an intramolecular version between ketoesters and vinyl ketones (Entry 1);[11a] (ii) the dimerization of **4** affording product **5** by the reaction of nucleophilic C-4 position of enol **4e** with the electrophilic C-3 position of the keto tautomer **4k** (Scheme 2 and Entry 2);[11b] (iii) the use of quinones as electrophiles in the vinylogous Michael addition of **4** to **6** resulting in the formation of compounds of type **7** (Scheme 2 and Entry 3);[11c] and (iv) the formation of polymers **10** by reaction of the bis-ketoester **8** with the bis-vinyl-ketone **9** (Scheme 2 and Entry 4).[11d]

Table 1. Iron-catalyzed Michael additions

Entry	Catalyst	Nucleophile	Electrophile	Others	Ref.
1	$FeCl_3{\cdot}6H_2O$	Ketoester	Vinyl ketone	Intramolecular	11a
2	$FeCl_3{\cdot}6H_2O$	Ketoester	Vinyl ketone	Vinylogous	11b
3	$FeCl_3{\cdot}6H_2O$	Ketoester Diketone	Quinones	Vinylogous	11c
4	$FeCl_3{\cdot}6H_2O$	Ketoester	Vinyl ketone	Polymerization	11d
5	$FeCl_3{\cdot}6H_2O$	Ketoester	Vinyl ketone oximes	Preparation of pyridines	12
6	Fe^{+3}-exchanged mica	Ketoester	MVK	Recoverable catalyst	13
7	Silica aerogel-ferrihydrite nanocomposite	Diketone	Azodicarboxylate	Recoverable catalyst	14



Scheme 2. Michael additions catalyzed by $FeCl_3{\cdot}6H_2O$ by Christoffers[11] and Tkachev.[12]

A further development has been reported by Tkachev's group[12] Thus, Michael addition of ketoesters to oximes of unsaturated ketones affords pyridines (Scheme 2 and Entry 5).
Iron(III) species have been used in solid supports. Thus, Fe^{+3}-exchanged fluorotetrasilicic mica catalyzes reactions of β-ketoesters with methyl vinyl ketone (MVK).[13] However, the catalyst is limited to this electrophile, but is recovered and reused (Entry 6).

Our group has reported the formation of silica aerogel–ferrihydrite nanocomposite as a recoverable catalyst in the Michael addition of acetylacetone to dialkyl azodicarboxylates and in the Biginelli reaction.[14] The catalytic solid can be reused without loss of activity (Entry 7).

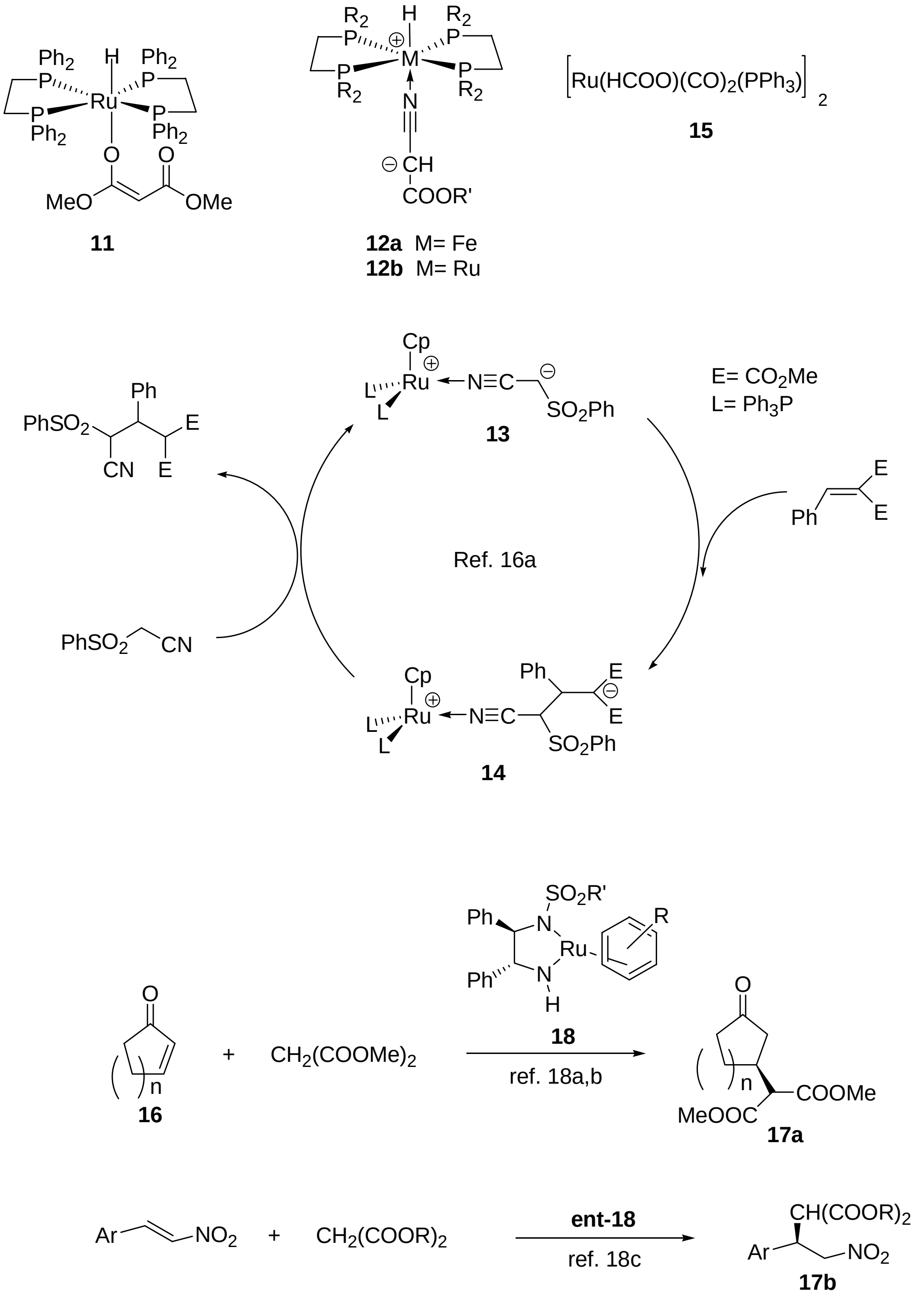
2.2 Group VIII. Ruthenium (Table 2)

Ruthenium species have been studied intensively. Komiya and his coworkers have reported the catalytic effect of the ruthenium(II) enolate **11**[15a] and iron(II)- and ruthenium(II)- complexes **12**[15b,c] in simple Michael additions (Entries 1 and 2). Similar results, based on the intermediacy of N-bound α-cyano-carbanions have been reported by Naota and Murahashi.[16] Binding of the nitrogen atom to ruthenium increases the acidity of active protons in a cyanosulfone to afford an isolable internal salt **13** (Scheme 3 and Entry 3). Salt **13** is catalytically active in the Michael reaction of the cyanosulfone with the arylmethylidenemalonate. Reaction of **13** with arylmethylidenemalonate gives **14**. The catalytic cycle shown in Scheme 3 has been suggested.[16]
A larger range of nucleophiles is effective under the action of catalyst **15** (Entry 4).[17] However, only MVK was tested as electrophile.

Reaction of 5-, 6-, and 7-membered unsaturated ketones **16** with malonates, ketoesters, and other nucleophiles affords compounds **17a** under catalysis by **18** with impressive enantioselectivity in the electrophile of up to more than 99% *ee* (Scheme 3 and Entry 5).[18a,b] In sharp contrast with the ruthenium enolate, **11**, the mechanism of these enantioselective reactions seems to involve insertion of the metal into the C-H bond of the nucleophile.[18a,b] In a related paper by the same group it was shown that Michael addition of several dicarbonyl compounds (Scheme 3 and Entry 6) to nitro-olefins gives **17b** with *ee*'s up to 98% under catalysis by **ent-18**.[18c]

Table 2. Ruthenium-catalyzed Michael additions

Entry	Catalyst	Nucleophile	Electrophile	*ee*	Ref.
1	**11**	Malonate Diketone	Acrylate Acrylonitrile		15a
2	**12a,b**	Cyanoacetate Cyanopropionate	Acrylonitrile		15b,c
3	**13**	Cyanosulfone Cyanoacetate Cyanopropionate Cyano ketone	Ylidenemalonate Ylidenemalononitrile Acrylate Acrolein Acrylonitrile		16a,b
4	**15**	Ketoester Diketone Malonate Cyanoacetate Nitroacetate	MVK		17
5	**18**	Malonate Ketoester Diketone Cyanoacetate Nitroacetate	Cyclic unsaturated ketones	In electrophile: > 99%	18a,b
6	**ent-18**	Malonate Ketoester Diketone	$ArCH{=}CHNO_2$	In electrophile: 98%	18c



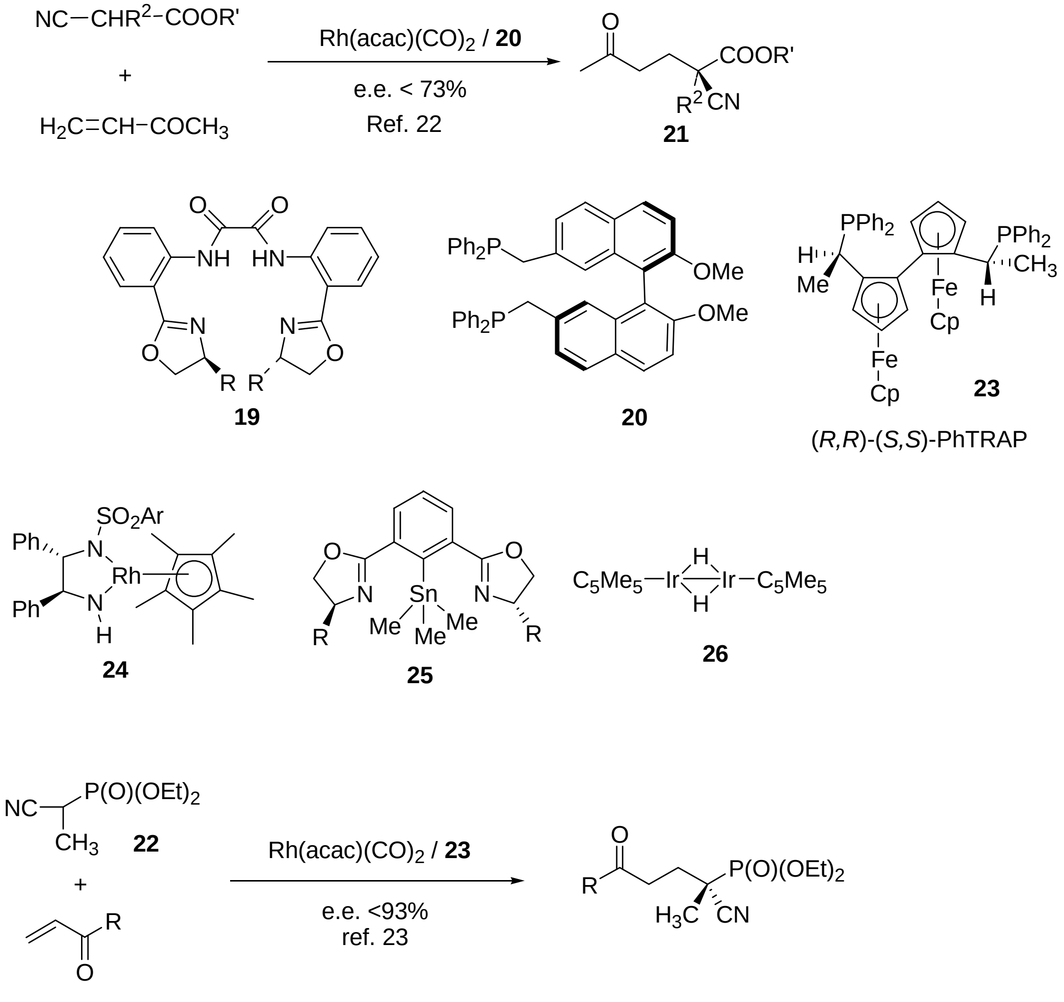
Scheme 3. Michael additions catalyzed by ruthenium species.

A note of warning should be introduced here. The alleged catalytic ability of $RuH_2(PPh_3)_4$ in Michael additions is due, at least in part, to free triphenylphosphine.[19]

2.3 Group IX. Cobalt, rhodium, and iridium (Table 3)

Cobalt species have been studied for a long time. Thus, Brunner and his co-workers screened several acetylacetonates in combination with (*S*,*S*)-1,2-diphenyl-1,2-ethanediamine in the reaction of a cyclic ketoester with acrolein. Among the metals studied (Co, Ni, Cu, Zn, La, Eu, Yb), cobalt was the best, although the *ee*'s were modest (Entry 1).[20]

Pfaltz and co-workers reported on the use of cobalt(II) acetate in the presence of chiral bis-(dihydro-oxazolylphenyl)oxalamides **19** (Scheme 4). The best *ee* was 89% (Entry 2).[21]



Scheme 4. Michael additions catalyzed by cobalt, rhodium, and iridium species.

The complex Rh(acac)$(CO)_2$ in combination with the enantiomerically pure diphosphine **20** promotes Michael addition of cyanopropionates to MVK to afford compounds **21** with modest *ee*'s at the nucleophile (Scheme 4 and Entry 3).[22] Insertion of rhodium into the C-H bond of the nucleophile was observed. Related results have been reported for the (1-cyanoethyl)phosphonate **22** (Entry 4).[23] Again, Rh(acac)$(CO)_2$ is the precursor of the catalytic species together with

(*R,R*)-(*S,S*)-PhTRAP, **23**. The configuration of the final product has only been assigned tentatively.

A rhodium(III) complex of probable structure **24** catalyzes Michael reactions of several cyclic and open ketoesters to MVK. *Ee*'s up to 75% (*S*- isomers) were secured (Entry 5).[24] Cyanopropionate and acrolein afford Michael adducts in up to 86% *ee* with a Rh(III) catalyst formed from the combination of RhCl(cyclooctene)$_2$ with the box-type chiral inductor **25** (Entry 6). However, ketoesters and nitro compounds are inert. Therefore, the cyano group seems to be essential.[25]

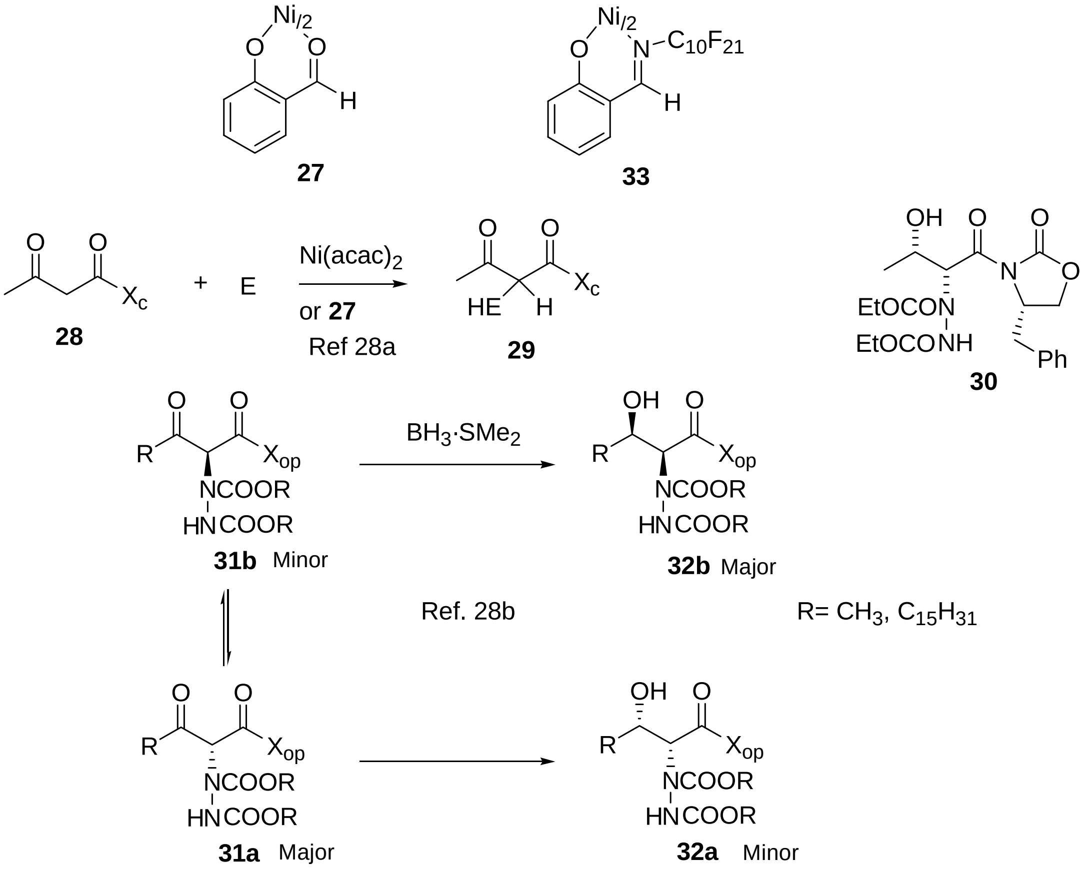
The binuclear iridium(II) dihydride complex **26** catalyzes the double Michael addition of ethyl acetoacetate and of ethyl cyanoacetate to acrylonitrile. This is a consequence of the high basicity of **26** which takes a proton from the pronucleophile (Entry 7).[26]

Table 3. Cobalt-, rhodium-, and iridium- catalyzed Michael additions

Entry	Catalyst	Nucleophile	Electrophile	*ee*	Ref.
1	Co(acac)$_2$/ (*S,S*)-[PhCH(NH$_2$)]$_2$	Cyclic ketoester	Acrolein	In nucleophile: 47%	20
2	Co(OAc)$_2$/**19**	Malonate	Chalcone	In electrophile: 89%	21
3	Rh(acac)(CO)$_2$/**20**	Cyanopropionate	MVK	In nucleophile: 73%	22
4	Rh(acac)(CO)$_2$/**23**	**22**	Vinyl ketone Acrolein	In nucleophile: 93%	23
5	**24**	Ketoester	MVK	In nucleophile: 75%	24
6	RhCl(*c*-octene)$_2$ /**25**	Cyanopropionate	Acrolein	In nucleophile: 86%	25
7	**26**	Ketoester Cyanoacetate	Acrylonitrile		26

2.4 Group X. Nickel (Table 4)

Nickel has been one of the preferred metals in catalyzed Michael reactions since the contribution of Nelson's group,[8] who reported on the catalytic activity of Ni(acac)$_2$. However, Nelson's catalyst has a shortcoming: it has a free inter-carbonyl position, and so it reacts at that position, C-3, of the pentane-2,4-dione moiety. This is a common feature of covalent metal complexes of β-dicarbonyl compounds.[27] To circumvent this problem we have introduced the nickel complex of salicylaldehyde, **27** (Scheme 5). This catalysts is as efficient as Ni(acac)$_2$ but does not give the side reactions of the original Nelson's catalyst.[28a] When Nelson's catalyst or the related **27** were applied to acetoacetates of chiral inductors, **28**, the resulting products **29** were obtained with diastereomeric excesses of up to 64% (82:18 diastereomeric ratio). This was enough to obtain reasonable overall yields (around 50% for two steps) of products such as **30** after reduction of the corresponding ketone featuring Evans' oxazolidinone as a chiral inductor (Scheme 5 and Entry 1 of Table 4).[28a]



Scheme 5. Michael additions catalyzed by Ni(acac)$_2$ and compound **27**.

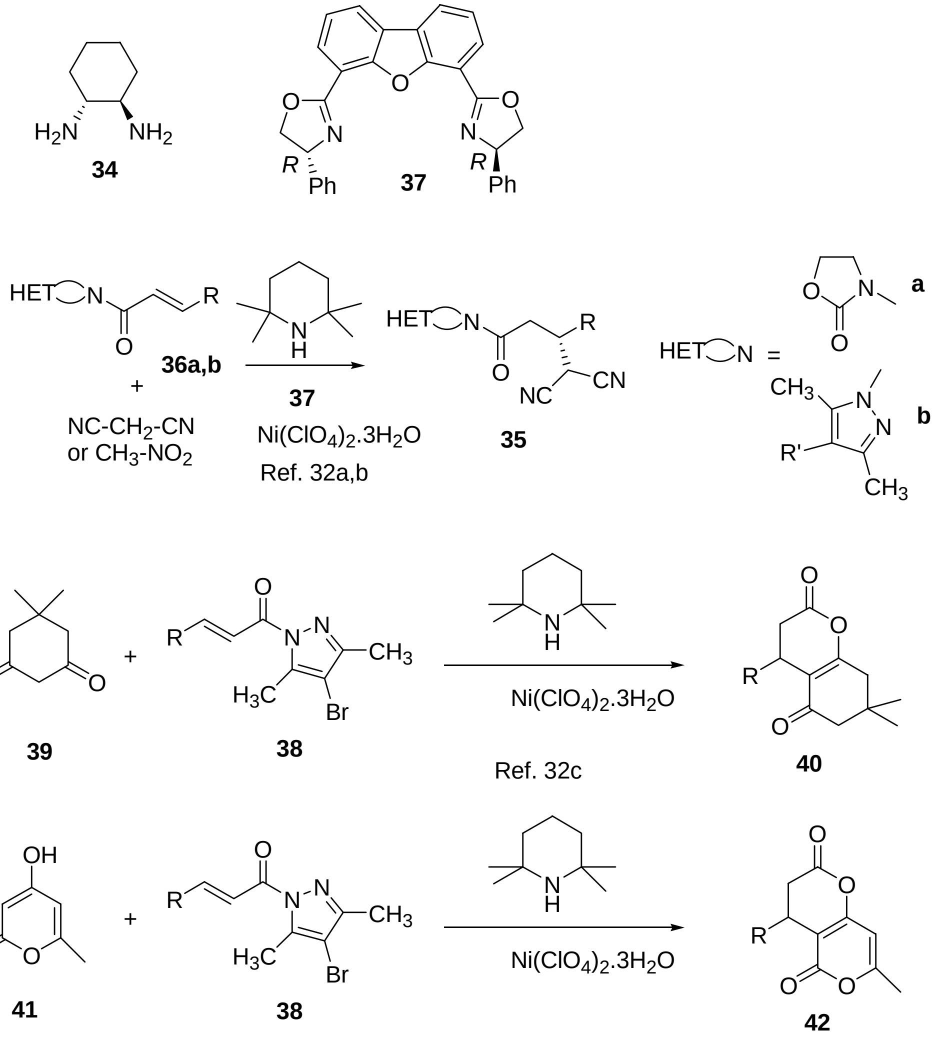
Table 4. Nickel-catalyzed Michael additions

Entry	Catalyst	Nucleophile	Electrophile	Comments	Ref.
1	**27**	Diketones Ketoesters Ketoamides	Vinyl ketones Azodicarboxylate 2-Vinylpyridine E-C≡C-E	*De* in nucleophile: 64%	28
2	**33**	Diketones	Azodicarboxylate	Organic-fluorous biphasic recovery of catalyst	29
3	$Ni(OAc)_2.4H_2O$/ **34**	Cyclic Ketoesters	Vinyl ketone	*ee* in nucleophile: 91%	31
4	$Ni(ClO_4)_2.3H_2O$/ **37**	$NCCH_2CN$ CH_3NO_2	Vinyl amides **36**	*ee* in electrophile: 98%	32a,b
5	$Ni(ClO_4)_2.3H_2O$	**39**, **41**	Vinyl amides **38**		32c

When Oppolzer's sultam was used as chiral inductor, the ketoamides **31a** were formed as major products, albeit with modest *de*'s (Scheme 5). However, upon reduction, a kinetic resolution gave **32b** as practically the sole products, only traces of diastereoisomers **32a** being present.[28b]

Complex **33** was tested as a recoverable catalyst in an organic–fluorous biphasic solvent system (Entry 2). The fluorous solution of **33** was recovered and re-used several times, but loss of activity was finally evident.[29]

Further studies on Nelson's catalysts include work in ionic liquid solvents aimed at recovery and re-use of the catalyst. Preliminary results suggested that $Ni(acac)_2$ was more active than iron(III) chloride hexahydrate and ytterbium triflate in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate, $[bmim][BF_4]$, in catalyzing the reaction of acetylacetone with MVK.[30a] However, more profound studies disclosed that the activity of the three mentioned catalysts, as well as the activity of $Co(acac)_2$, is strongly dependent on the presence of chloride ion, a typical impurity in ionic solvents.[30b]



Scheme 6. Michael additions catalyzed by other nickel species.

Other studies based on nickel catalysis aimed at generating enantioselectivity. Thus, reaction of cyclic β-ketoesters with MVK produced *ee*'s as high as 91% in the nucleophile when catalyzed by the pair nickel acetate and diamine **34** (Scheme 6 and Entry 3).[31] On the other hand, Kanemasa and co-workers have obtained high *ee*'s (up to 94%) in the electrophile in the preparation of **35** from malononitrile or nitromethane and the vinyl amides **36** under double catalytic activation conditions using the pair nickel perchlorate and a box-type chiral inductor **37** (Scheme 6 and Entry 4).[32a,b]

Another application of the double catalytic activation conditions, described by the same authors, is the reaction of **38** (a particular example of **36b**) with either cyclic six-membered β-diketones of type **39** or triacetic acid lactone, **41**, and related lactones to afford bicyclic compounds such as **40** and **42** (Scheme 6 and Entry 5).[32c] The pyrazole moiety acts as a pseudo-halogen leaving group after the initial Michael addition.

2.5 Group X. Palladium and platinum (Table 5)

Table 5. Palladium- and platinum- catalyzed Michael additions

Entry	Catalyst Metal	Nucleophile	Electrophile	Others	Ref.
1	**43** Pt	Cyanopropionate	Vinyl ketone	Low *ee* in nucleophile	33
2	**44** Pd	Ketoesters Diketones	Vinyl ketone	*ee* in nucleophile: 99%	34a
3	**44** Pd	Ketoesters	Vinyl ketone	In ionic liquid. Recoverable catalyst	34b
4	**46** Pd, Pt	Cyanoacetate Cyanopropionate Nitromalonate	Vinyl ketone Acrylonitrile		35
5	Pd/N,C,N pincer ligands	Cyanoacetate	Vinyl ketone		36a
6	Pd/P,C,P' pincer ligand	Cyanoacetate	MVK		36b
7	Pt/N,C,N' pincer ligand	Cyanoacetate	MVK	Encapsulation in amphiphilic polyglycerol nanocapsules	36c,d
8	Pd/N,C,N' pincer ligands	Cyanopropionate	Vinyl ketone	*ee* in nucleophile: 83%	37
9	Pd/N,N',N'' pincer ligand	Cyanopropionate	MVK	*ee* in nucleophile: 43%	38

Examples of catalysis by other metals of Group X appeared much later than those described so far. Probably the first example is the addition of 2-cyanopropionate to MVK catalyzed by the cationic platinum complex **43**. *Ee'*s generated with the nucleophile were low (Entry 1, Scheme 7).[33]

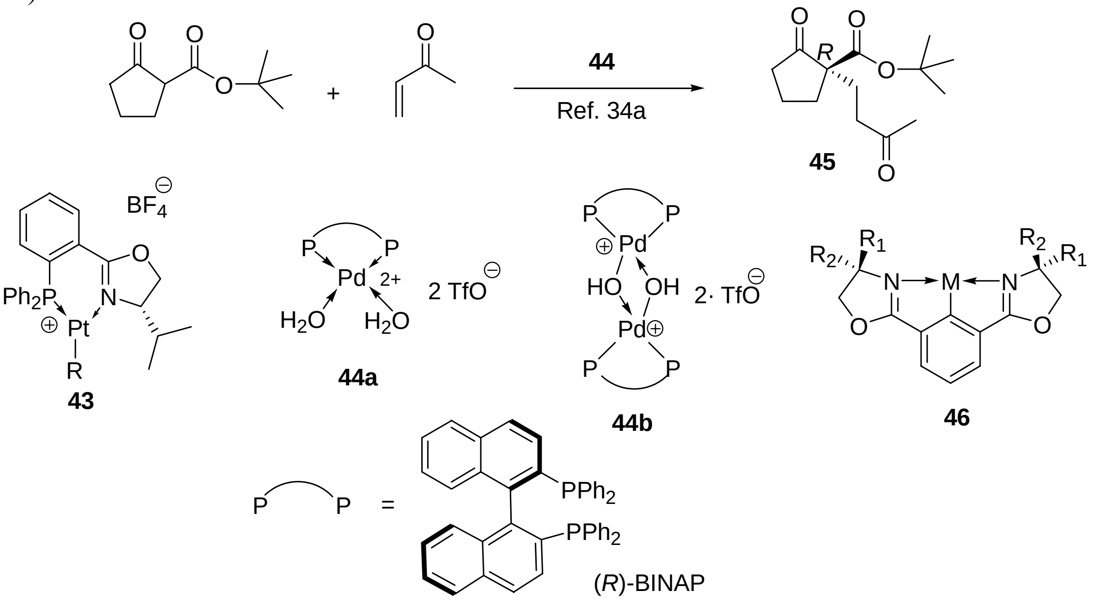
Better results were secured by Sodeoka and his co-workers by using the cationic palladium complex **44a** and the related bridged dimer **44b** (Scheme 7 and Entry 2), both based on (*R*)-BINAP or (*R*)-Tol-BINAP. Several open- and cyclic diketones and ketoesters afforded compounds of type **45** with high *ee'*s that in some cases reached 99%.[34a] This paper includes a mechanistic study by ^{1}H- NMR and Electrospray Ionization Mass Spectrometry (ESI-MS) that will be commented upon later.

The same catalysts **44** were tested in ionic solvents (Entry 3). The percentage recovery of the catalysts was promising but not excellent.[34b]

In a series of papers, Richards and his co-workers presented their results on the use of pincer-palladium and -platinum complexes **46** and related structures as catalysts in the Michael addition of cyanoacetates to MVK and acrylonitrile (Entry 4). The *ee'*s were modest.[35] The catalytic action has been related to the Lewis acidity of the metal center in the complexes. The reactions also required a catalytic amount of Hunig's base.

Other palladium complexes of N,C,N' and P,C,P' pincer ligands have been tested in the same model reaction between cyanoacetate [36a,b] (Entries 5 and 6) or cyanopropionate [37] (Entry 8) and MVK. In the last case the enantiomerically pure ligand led to *ee'*s in the final product. A platinum complex of a N,C,N' pincer ligand encapsulated in amphiphilic hyperbranched polyglycerol nanocapsules has also been tested with the standard reaction between cyanoacetate and MVK (Entry 7).[36c,d]

Other structurally related ligands featuring a pyrrole- based structure did not improve the *ee's* (Entry 9).[38]



Scheme 7. Michael additions catalyzed by palladium and platinum species.

2.6 Group XI. Copper and Silver (Table 6)

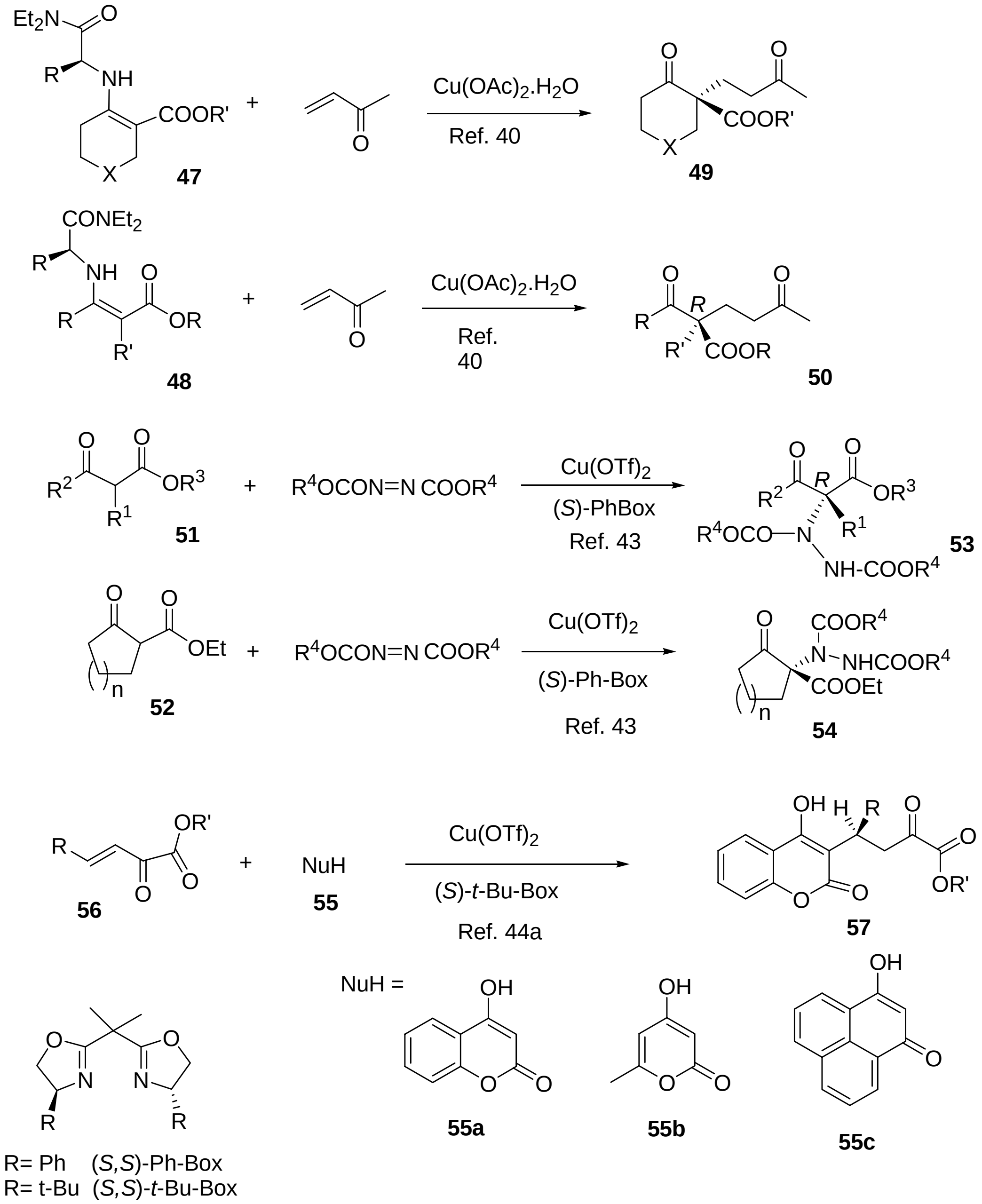
Copper is probably the transition metal that has attracted most attention as a catalyst in Michael additions after the pioneering work by Saegusa's group.[7] Two groups have studied enantioselective Michael additions adopting two different strategies. Thus, Christoffers' group performed a general screening of catalysts in enantiomerically pure surroundings, *i.e.*, in the presence of chiral ligands.[39] They concluded that copper(II) acetate monohydrate is an excellent catalyst in terms of chemical efficiency, although the *ee's* had to be improved.

Improved results by the same group came out soon afterwards. Thus, chiral enamines **47** of cyclic- (X = CH_2,[40a,b,c], X = NBoc[40d]) and open- ketoesters,[40c] **48**, react with MVK under copper acetate monohydrate catalysis to afford compounds **49** and **50** with excellent *ee*'s (Scheme 8 and Entry 1). Although these contributions are limited to MVK as electrophile, some of the enamines (**47**, X = NBoc) are starting points for further interesting synthetic elaboration of the enantiomerically pure decahydro-6-isoquinoline scaffold.[41]

Table 6. Copper-catalyzed Michael additions

Entry	Catalyst	Nucleophile	Electrophile	Others	Refs.
1	$Cu(OAc)_2.H_2O$	Enamines **47** and **48**	MVK	*ee* in nucleophile: 98%	40, 41
2	$Cu(OTf)_2$/Ph-Box	Ketoesters	Azodicarboxylate	*ee* in nucleophile: 99%	43
3	$Cu(OTf)_2$/*t*-Bu-Box	Ketolactones and diketones **55**	**56**	*ee* in electrophile: 98%	44a
4	$Cu(OTf)_2$/Ph-Box	Ketoester	Azodicarboxylate	*ee* in nucleophile: 99%	45
5	$Cu(SbF_6)_2$ **61,** salicylaldehydate **62**	Ketoester Diketone	MVK Acrylonitrile Acrylate Azodicarboxylate Quinone	Mechanistic studies	46
6	$CuSO_4.5H_2O$	Diketone	Unsaturated ketone		47

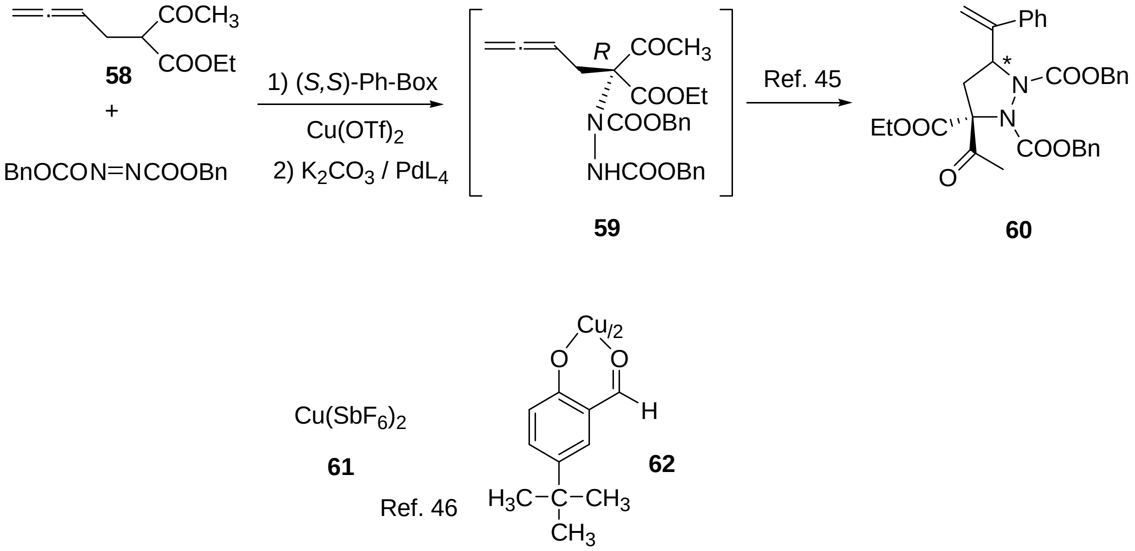
Other enamines featuring the chiral amine moiety in the lateral side have been also evaluated.[42] Although interesting *ee*'s have been realized, the preparation of such chiral enamides is more difficult than that of the compounds **47**.



Scheme 8. Michael additions catalyzed by copper species.

A different approach has been adopted by Jørgensen and his co-workers. Thus, the combination of copper triflate and Ph-Box induces spectacular *ee*'s in the reactions of the open- and cyclic ketoesters **51** and **52** with azodicarboxylates (Scheme 8 and Entry 2). Products **53** and **54** were prepared in *ee*'s up to 99% in the nucleophile.[43] Moreover, *ee*'s up to 98% in the electrophile were achieved by the same group when lactones **55a,b** or diketone **55c** react with the unsaturated ketone **56** that also possesses an ester function (Entry 3).[44a] The high *ee*'s observed for **56** are probably related to the α-ketoester structure, as pointed out in paragraph 5. Indeed, reaction of α-ketoesters with azodicarboxylates also affords *ee*'s of 96% in the nucleophile under catalysis by copper triflate and Box- type inductors.[44b]

Related work by Ma and co-workers includes the initial reaction of the ketoester **58** with azodicarboxylate under catalysis by the pair copper triflate–Ph-Box (Scheme 9 and Entry 4). The intermediate **59** reacts *in situ* with iodobenzene under palladium catalysis to afford mixtures of the diastereoisomers **60** at the position marked with the asterisk. Enantioselectivity at the inter-carbonyl position was high for both diastereoisomers (up to 99%).[45]



Scheme 9. Michael additions catalyzed by copper species.

Both copper(II) hexafluoroantimonate, **61**, and copper(II) 5-*t*-butylsalicylaldehydate, **62**, are examples of ionic and covalent copper catalysts which are active over a broad range of combinations of nucleophile–electrophile (Scheme 9 and Entry 5).[46] Both catalysts share a common feature: they form *in situ* the copper complex of the nucleophile, which is supposed to be the active species of the reaction (*vide infra*).

Another report describes the catalytic effect of pentahydrated copper sulfate (Entry 6).[47]

It seems that only one paper has been published on silver- catalyzed Michael additions. Thus, Kobayashi has reported the Michael additions of β-ketoesters to unsaturated ketones in water and in the presence of silver triflate and BINAP derivatives.[48] Promising enantiomeric excesses were observed.

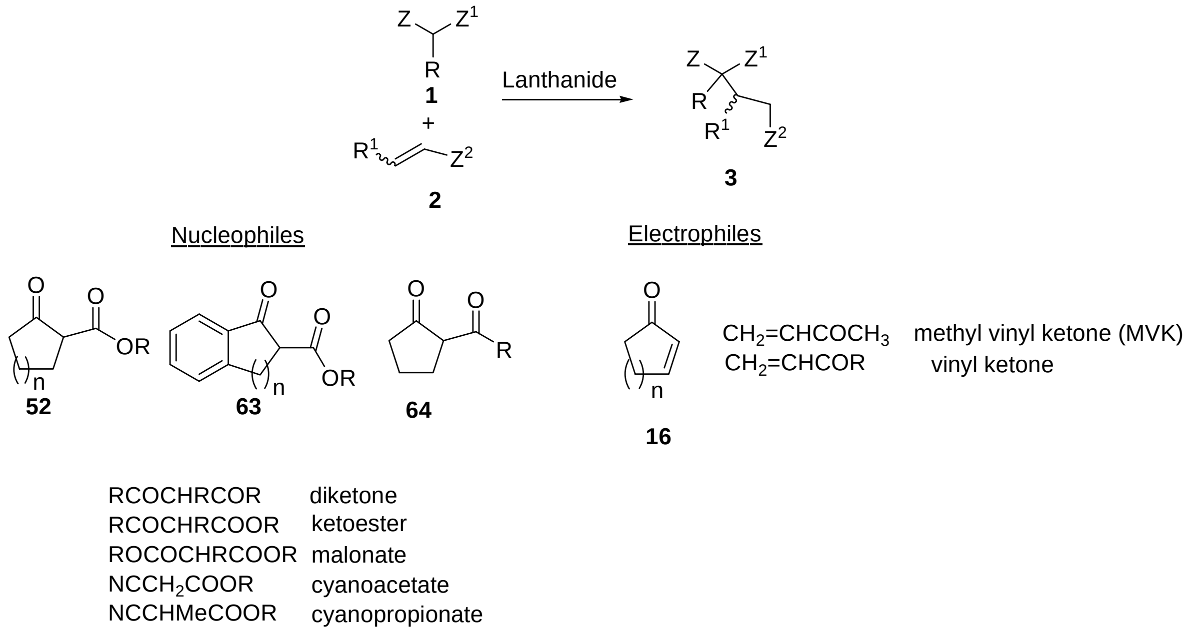
2.7 Other metals and special procedures

Some other metals outside the scope of this review are also active in Michael additions. Thus, bismuth(III) chloride and cadmium(II) chloride have been reported to catalyze the Michael addition of simple diketones, ketoesters, and malonates to MVK and to chalcone under microwave irradiation,[49] and indium(III) chloride is active in the Michael addition of 1,3-dicarbonyl compounds to unsaturated ketones.[50]

Microwave irradiation accelerates the Michael addition of diketones, ketoesters, and malonates to MVK under catalysis by the acetylacetonates of Cr(III), Mn(II), Fe(III), Co(II), Ni(II), and Cu(II).[51]

3. Catalysis of Michael additions by lanthanide species

The lanthanides are a group of metals which have peculiar characteristics — mainly their expanded coordination index, the contraction of their ionic radii as the atomic number increases (“the lanthanide contraction”), and the stability of their triflates in water. A useful paper on asymmetric catalysis by lanthanide complexes discusses these characteristics very well.[52]



Scheme 10. General Michael addition.

Several terms frequently encountered in this part of the article are presented in Scheme 10. Scandium will be, rather arbitrarily, be considered with lanthanides.

Although transition-metal derivatives have been used for a long time as catalysts in Michael additions, the use of lanthanide derivatives is much more recent. Possibly the first report was one by Scettri and his co-workers who reported the Michael addition of β-diketones or β-ketoesters to α,β-unsaturated ketones catalyzed by europium(III) chloride hexahydrate and by certain europium(III) β-diketonates.[53]

3.1 Scandium (Table 7)

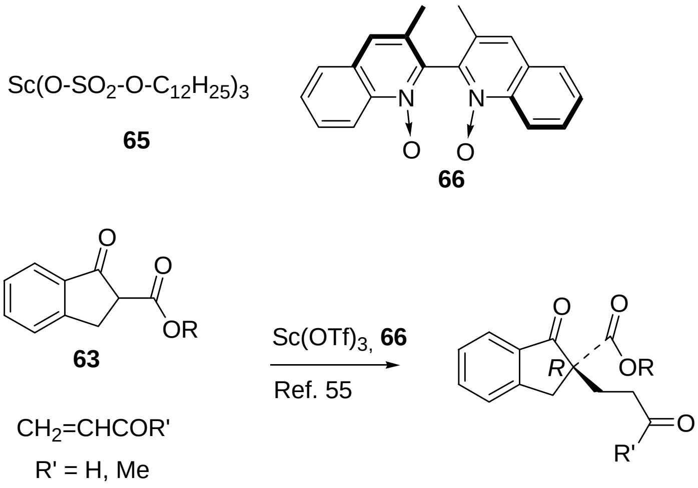
Kobayashi's group performed a screening of several lanthanides and copper derivatives, mainly in the form of anionic surfactants.[54] They found that scandium tris(dodecyl sulfate), STDS, **65** was an excellent catalyst for the reaction of cyclic **52**, **63**, and open ketoesters with MVK and cyclopentenone, **16** (n=1) in water (Entry 1). The catalytic activity in water was found to be higher than in organic solvents (*vide infra*).

The reaction of the cyclic compound **63** with MVK or with acrolein was catalyzed by scandium triflate in the presence of this chiral bis-*N*-oxide **66** (Scheme 11 and Entry 2). The method failed for ethyl acrylate.[55] The maximal *ee* was 84%.

Table 7. Scandium-catalyzed Michael additions

Entry	Catalyst	Nucleophile	Electrophile	Others	Ref.
1	$Sc(OSO_2\text{-}C_{12}H_{25})_3$, **65**	**52** (n=1,2) **63** (n=1) Ketoester	MVK **16** (n=1)	Surfactant in water	54
2	$Sc(OTf)_3$ / **66**	**63** (n=1,2)	MVK acrolein	*ee* in nucleophile: 84%	55
3	Sc-montmorillonite	**52** (n=1,4), **64** Ketoester Diketone Malonates	Vinyl ketones **16** (n=1,2) Acrylates	Recovery and reutilization of catalyst in water	56

The most versatile method involving scandium is that reported by Kaneda on the use of scandium(III)-doped montmorillonite. A broader range of nucleophiles — open-chain ketoesters, diketones, malonate, as well as the cyclic compounds **52** and **64** — react with vinyl ketones, cyclic or not, and with ethyl acrylate (Entry 3).[56] The reactions are performed either in water or without solvent, and the catalyst was recovered and re-used three times without lose of activity. It is postulated that simultaneous coordination of the nucleophile enolate and of the electrophile is essential for the good activity.



Scheme 11. Michael additions catalyzed by scandium species.

3.2 Lanthanum (Table 8)

Table 8. Lanthanum-catalyzed Michael additions

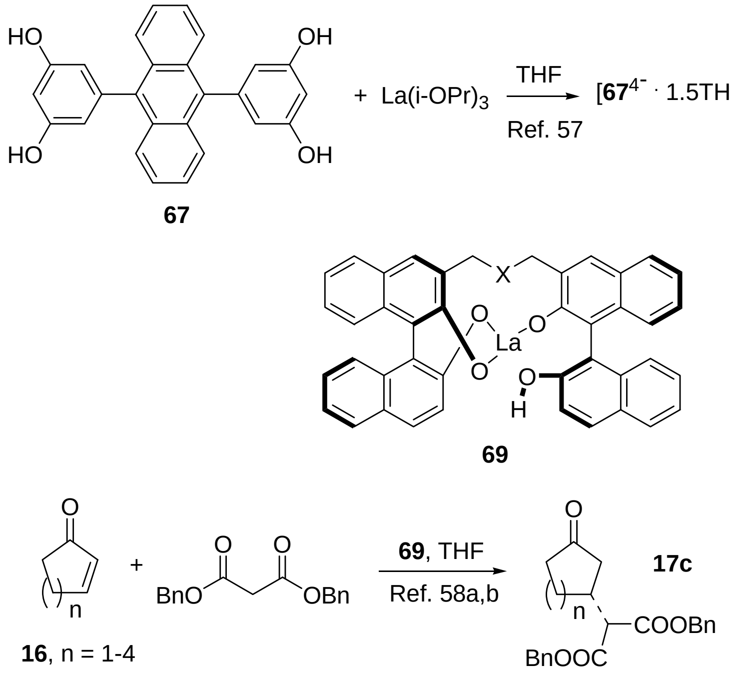
Entry	Catalyst	Nucleophile	Electrophile	Others	Ref.
1	**68**	Malonate	**16** (n = 2)		57
2	**69**	Malonate Methylmalonate **52** (n = 2)	MVK Vinyl ketones **16** (n = 1-4)	*ee* in electrophile: 99% *ee*	58

The reaction of the tetraphenol **67** with lanthanum triisopropoxide produces an insoluble solid of composition **68**. This solid is a heterogeneous catalyst for the Michael addition of malonate to cyclohexenone, **16**, in benzene (Scheme 12 and Entry 1).[57]

The most remarkable results obtained with lanthanum species are those by Shibasaki's group. Thus, complexes based on linked-BINOL, **69**, are excellent enantioselective catalysts for the Michael addition of malonate, methyl malonate, and the cyclic β-ketoesters **52** (n = 2) to α,β-unsaturated ketones, both cyclic [5- to 8-membered (**16**, n = 1–4)] and non-cyclic (Scheme 12 and Entry 2).[58] For X = O the *ee* reached up to >99%.[58a,b] The authors propose the formation of the lanthanum enolate with simultaneous coordination of the electrophile. In another paper on this series a screening of different metals as well as of different linking units (X = S, NH, NR) is described.[58c] This last paper presents data obtained by Electrospray Ionization Mass Spectrometry (ESI-MS). A species containing lanthanum, the ligand **69**, and the ketoester was identified, thus reinforcing the mechanistic hypothesis of the metal enolate as an active entity.

Immobilization of the ligand in an organic polymer leads to a decreased activity.[58c]

The adduct **17c** (n = 2) was converted into an advanced intermediate in a synthesis of strychnine.[58d]



Scheme 12. Michael additions catalyzed by lanthanum species.

3.3 Cerium and samarium (Table 9)

Bartoli’s group has published a review on the catalytic properties of cerium(III) chloride heptahydrate.[59] This review includes Michael and hetero-Michael additions.

Table 9. Cerium and samarium catalyzed Michael additions

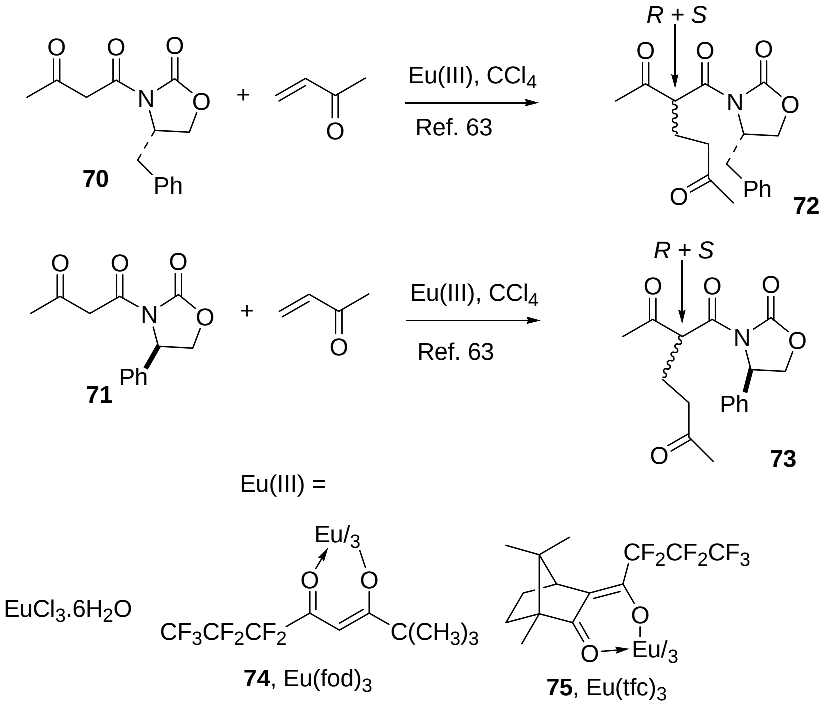
Entry	Catalyst	Nucleophile	Electrophile	Others	Ref.
1	$CeCl_3 \cdot 7H_2O$/NaI	Diketone Ketoester	MVK **16** (n = 1,2) Acrolein Cinnamaldehyde	Only one mol. of electrophile was introduced	60
2	$CeCl_3 \cdot 7H_2O$	Diketone Ketoester Malonate **63, 64**	MVK **16** (n = 2) Chalcone	Microwave Irradiation	61
3	SmI_3	Malononitrile Cyanoacetate Malonate Ketoester Nitromethane	Chalcones		62

The same group has reported Michael additions catalyzed by the pair cerium(III) chloride heptahydrate and sodium iodide in the absence of solvent.[60] The active nucleophiles are open chain diketones and ketoesters, and the electrophiles were MVK, **16** (n = 1,2), acrolein, and cinnamaldehyde (Entry 1). The reactions stop after the introduction of only one mole of electrophile. Thus, the proposed catalyst can be useful if no contamination by the product of double reaction is required.

Microwave activates the $CeCl_3{\cdot}7H_2O$-catalyzed solvent-free Michael additions (Entry 2).[61] Promoted by samarium(III) iodide, malononitrile, cyanoacetate, malonate, ketoester, and nitromethane react with unsaturated ketones [62a,b] and esters (Entry 3).[62c]

3.4 Europium

Scettri and his co-workers, as a continuation of their pioneering work, have reported a different strategy aimed at the induction of selectivity. They prepared the acetoacetamides **70** and **71**, featuring Evans' oxazolidinone chiral inductors. The *de*'s in the products from addition to MVK were modest and epimerization upon purification of final products **72** and **73** was noticed (Scheme 13).[63] Europium chloride hexahydrate or the europium enolates **74** and **75** were useful catalysts.



Scheme 13. Michael additions catalyzed by europium species.

3.5 Ytterbium

Ytterbium triflate ($Yb(OTf)_3$) catalyzes Michael additions of ketoesters **52** (n = 2) to ethyl acrylate.[64a] However, the authors report also that triflic acid is a more general catalyst.

Comparative studies [using Ni(acac)$_2$, iron(III) chloride hexahydrate, ytterbium triflate, and Co(acac)$_2$] in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate [bmim][BF$_4$]) in the reaction of acetylacetone with MVK, have been discussed in paragraph 2.4.[30]

4. Evaluation of the synthetic methods

The present paper collects the abundant information published since 1997–1998 until November 2004. A critical analysis of such information could be helpful. Many different combinations of metals and ligands seem to offer interesting alternatives to the classical catalysis by bases. However, a closer scrutiny reveals some limitations.

Sometimes researchers are interested in a synthetic method without regard to enantioselectivity. It is immediately obvious that in this paper we have dealt with catalysts ranging from very simple to very complicated. The old catalysts used by Saegusa [7] (Cu_2O/:C=N-C_6H_{11}) and Nelson[8] [Ni(acac)$_2$, probably as the dihydrate] are sufficiently simple and of general applicability to fulfil many current needs. Later, many simple metal salts and complexes have been reported to be active catalysts — iron(III) chloride hexahydrate,[11] cobalt(II) acetate,[21] nickel salicylaldehydate, **27**,[28] nickel acetate tetrahydrate,[31] nickel perchlorate trihydrate,[32] copper acetate monohydrate,[40,41] copper triflate,[43–45] copper hexafluoroantimonate,[46] copper(II) 5-*t*-butylsalicylaldehydate,[46] and copper sulfate pentahydrate.[47] Clearly, these simple compounds offer better initial alternatives than the more complicated catalysts based on ruthenium, rhodium, palladium, or platinum.

Many reported reactions are limited to very active electrophiles such as MVK and azodicarboxylates. Some of those papers should be considered as basic studies on the properties of more- or less- exotic metal complexes, rather than as contributing a new general catalyst which can improve an already existing synthetic method. Many references deal only with a single model reaction used to test the catalytic properties of a given metal derivative.

Among the simple iron-, cobalt-, nickel-, and copper- catalysts we find compounds which are soluble in water and compounds which are soluble in organic phases. Therefore, in the opinion of these reviewers, they constitute the first choices for workers not familiar with this field.

If enantioselectivity has to be considered, possibly the most spectacular results are those reported by Jørgensen's group, because they combine the simplicity of the reagents and chiral inductors with the generality of the nucleophiles. Thus, several ketoesters — both open (**51**) or cyclic (**52**) — react with azodicarboxylates with convincing *ee*'s in the nucleophile, under catalysis by copper triflate and the commercially available (*S*)-Ph-Box (See Scheme 8 and Table 6, Entry 2).[43] Ma's group has reported similar excellent results with related nucleophiles and azodicarboxylates (Scheme 9 and Table 6, Entry 4).[45] Similar results from two independent groups induce us to believe that the combination Cu(OTf)$_2$/Ph-Box is the pair of choice. A broader array of electrophiles is desirable since azodicarboxylates are very active. Moreover, very high *ee*'s are obtained, this time at the electrophile, in the reaction between nucleophiles of different natures, **55**, and electrophiles **56** (Scheme 8 and Table 6, Entry 3).[44a] However, the peculiar structures of **56** open the question whether the generalization of the excellent high *ee's* to other electrophiles is possible or not (*vide infra*).[44]

There are other strategies that offer interesting possibilities. Thus, the temporary introduction of chirality in the form of enamines derived from chiral amines or amino-acid derivatives is the solution found by Christoffers' group. They have reported remarkable results in the preparation of **49** and **50** (Scheme 8 and Table 6, Entry 1).[40,41] However, only MVK is reported as the electrophile.

We have described the introduction of chirality in the nucleophile in the form of β-ketoamides of chiral inductors such as Evans' oxazolidinones or Oppolzer's sultam (Scheme 5 and Table 4, Entry 1). Although the *de*'s were never considerable, further synthetic work permitted isolation of enantiomeric final products in interesting overall yields.[28]

Remarkable *ee*'s from cyclic- and open-chain- electrophiles featuring different activating groups have been realized by Ikariya and his co-workers, using catalysis by ruthenium complexes **18** (Scheme 3 and Table 2, Entries 5 and 6). Since the range of nucleophiles is broad, this method is possibly the most general for inducing enantioselectivity at the electrophile.[18]

Excellent *ee*'s at the electrophile have also been reported by Kanemasa's group, by using nickel perchlorate trihydrate and the relatively simple inductor **37** (Scheme 6 and Table 4, Entry 4).[32] However, the range of nucleophiles is limited to malononitrile and nitromethane.

Other applicable results are those of Sodeoka's group (Scheme 7 and Table 5, Entry 2) based on palladium-(II) complexes of the available BINAP.[34a] However, only vinyl ketones are reported as electrophiles.

All the above methods look very simple and can be applied by any practitioner in the field. Other methods can look more complicated, but of course this view is a subjective one.

Although lanthanides are in their infancy as catalysts for the Michael reaction, we believe that their possibilities will be explored further in the future. Several lanthanide derivatives seem to offer interesting alternatives to the more classical catalysis by bases. However, closer scrutiny reveals limitations and it is immediately obvious that transition metals offer today broader applicability. The excellent enantioselection obtained by using the lanthanum complexes **69** — thanks to the work by Shibasaki and co-workers [58] — renders this method a good candidate for generating *ee* in the electrophile. Comparison of the relative merits of transition metals and lanthanides will be possible only when many investigations, already made with transition metals, have been made with lanthanides.

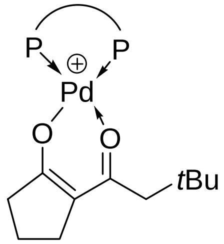
The strategy adopted by Scettri's group, which generates diastereoselection,[63] is worthy of further exploration.

5. Comments on mechanisms

Although great efforts have been devoted to the synthetic and selectivity aspects of Michael reactions catalyzed by transition metals, less effort has been dedicated to the mechanistic aspects, which are crucial for their better understanding.

We feel that metals such as ruthenium and rhodium operate by mechanistic rules different from iron or the "later" transition metals. Thus, ruthenium enolates **11** [15a] or hydrides **12a,b** [15b,c] have been identified as intermediates in Michael additions. This implies oxidative addition on the O-H or the C-H bond of the enol or keto forms of the nucleophile. The cycle in Scheme 3 has been proposed by Murahashi and co-workers for the Michael addition of many nitrile-activated methylene groups to Michael acceptors.[16] The presence of nitriles, which show strong ability to coordinate ruthenium, makes this type of mechanism possible. An important point is the increased acidity of the CH_2 protons upon nitrogen- coordination to ruthenium. Obviously this behavior is not extendable to other activating functional groups.

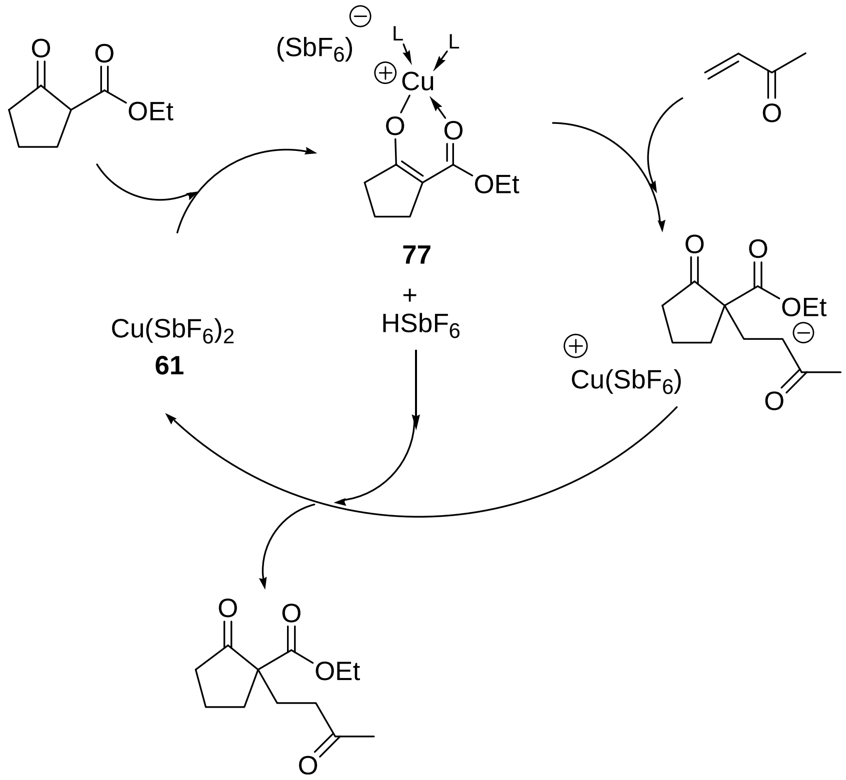
Coordination of the metal to the nucleophile as well as to the electrophile has frequently been invoked in this type of chemistry. Probably Sodeoka and his co-workers were the first to provide convincing evidence by NMR and Electrospray Ionization Mass Spectrometry (ESI-MS) of the formation of the palladium enolate **76** (Figure 1) in the reactions given in Table 5 (Entry 2).[34a] However, they found that the reaction did not proceed, because the palladium diketonate complex **76** is very stable. Addition of TfOH was needed for the reaction to proceed further (*vide infra*).



76

Figure 1

We have studied in depth the mechanism of Michael additions with copper-based catalysts, both ionic, with $Cu(SbF_6)_2$, **61**, or covalent, with the copper-(II) salicylaldehydate **62**. A detailed analysis by infrared and visible spectroscopies as well as by ESI-MS permitted us to propose the catalytic cycles of Schemes 14 and 15.[46] They have as a common feature the intermediacy of copper(II) enolates such as **77** (Scheme 14) and **78** (Scheme 15), formed *in situ* independently of the copper source. Therefore, the *in situ* generation of metal β-dicarbonyl enolates is now founded on a firmer basis.

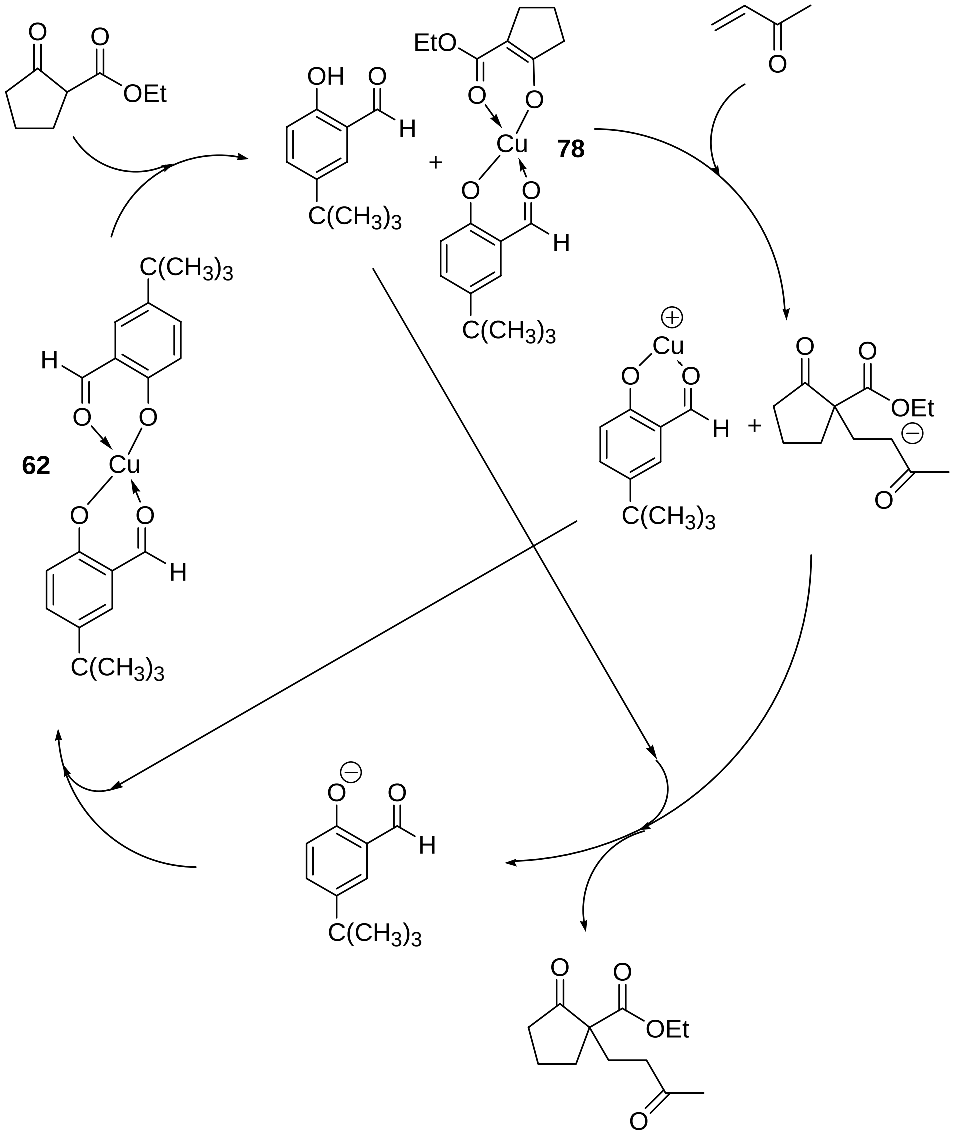


Scheme 14. Proposed catalytic cyclic for $Cu(SbF_6)_2$ catalyst.[46]

It is difficult to generalize the mechanistic results obtained for a particular reaction to other reactions featuring different metals, salts, complexes, or even reacting partners. However, other studies performed with iron salts suggest also the action of metal enolates as intermediates. Christoffers has studied the mechanism of the reaction between the cyclic ethyl ketoester **52** (n = 1) and MVK, catalyzed by $FeCl_3{\cdot}6H_2O$.[65] The reaction is first-order in iron, which is compatible with a one-center template reaction. The authors suggested simultaneous coordination of iron with the enolate and the carbonyl group of the electrophile. Added chloride anion inhibits the reaction, owing to competing coordination of chloride and the enolate. They therefore proposed the use of $Fe(ClO_4)_3{\cdot}9H_2O$ as a more efficient catalyst.

Direct experimental evidence of the *in situ* formation of iron enolates has been provided recently by an ESI-MS study.[66] Moreover, ions containing iron and neutral, non-deprotonated ketoesters are also formed under ESI-MS conditions.

In 1998 Kobayashi reported a striking correlation between the catalytic activity for the Mukaiyama aldol reaction in water and the hydrolysis constants of inner-sphere water ligands. He concluded that Lewis-acid- catalyzed reactions should be successful in water.[67]



Scheme 15. Proposed catalytic cyclic for copper salicylaldehydate **62** as catalyst.[46]

Recently, Spencer and his co-workers gave evidence that protons can be the active catalysts in Lewis-acid- mediated hetero-Michael addition reactions, by accelerating the enolization process.[68] They speculated on why so many metals, so different in nature, share the ability to catalyze hetero-Michael reactions. Their work is centered on nitrogen-based nucleophiles. On giving answers to this question they came to the conclusion, experimentally supported, that protons from water can be responsible for the common catalytic effects. Indeed, water increases in acidity when coordinated to metal. Those metals presenting lower pK (higher [H^+]) in the equation are the more active as catalysts in the studied reactions,

$$M^{n+} + H_2O \rightleftharpoons [M(OH)]^{(n-1)+} + H^+$$

A careful analysis of the reports in this review led us to at least three comments compatible with Spencer's analysis:

(i) Christoffers states that, *"Fe(acac)$_3$ and anhydrous FeCl$_3$ are significantly less active than the hexahydrate"* $FeCl_3 \cdot 6H_2O$.[3,65]

(ii) Kanemasa declares that, *"…complex derived from Ni(ClO$_4$)$_2$·6H$_2$O was the most effective catalyst and the aqua complex A showed both a much higher reactivity and greater selectivity than the anhydrous complex catalysts R,R-DBFOX/Ph.Ni(ClO$_4$)$_2$"*.[32b] The sentence refers to Table 4, Entry 4.

(iii) Sodeoka realized that complex **76** is not active: *"…the reaction did not proceed, probably because palladium diketonate complex is very stable. Interestingly, however, the addition of 1 equiv. of TfOH was found to be effective to promote the reaction"*. [34a]

Lanthanides have increased coordination numbers. This makes them ideal for simultaneous coordination of both reacting partners as well as ancillary chiral ligands around the metal. This is important when enantioselectivity is considered. Recently Shibasaki and his co-workers found ESI-MS evidence for the simultaneous coordination of the chiral ligand and a ketoester in the form of the enolate.[58c]

Lanthanide triflates are stable in water, and therefore this solvent is frequently used for the reactions mentioned in this review.[54,56] A careful analysis of the papers reviewed here led us to the following remarks:

i. Many reactions are made in water, as indicated in the tables, and some of the catalysts are hydrated forms of lanthanide salts.

ii. Kobayashi and his co-workers [54] mention that, *"The catalytic activity in water was found higher than that in organic solvents"* They refer to the scandium-catalyzed reactions of Table 7, Entry 1.

iii. In a preliminary communication on the catalytic effect of ytterbium(III) triflate Kotsuki's group points out that, *"An efficient Michael addition between **1** and **2** (1.5 eq) was accomplished at high pressure with the addition of a small amount of water."* [64b] Kotsuki's compounds **1** and **2** are, in this review, **52** (n = 1, R = Et) and **16** (n = 1). The possibility that a proton is the actual catalyst is reinforced by the fact that in a later paper the same authors report on the catalytic effect of triflic acid in many Michael reactions.[64a]

It should be mentioned here that Spencer and his co-workers reported that the strong acid Tf_2NH catalyzes the reactions which are supposedly catalyzed by metals.[68]

It is not unreasonable to think that Spencer's mechanism operates partially in some of the reactions discussed in this review. This ought to have a deleterious effect on the enantioselectivity of the reactions, since protons act outside the coordination sphere of the metal. Another interesting point raised by Spencer's paper is that dicarbonyl electrophiles have a strong propensity to coordinate metals through both carbonyl groups at the same time. This strong coordination can overcome the proton effect, mainly if water is eliminated carefully. This can be a factor contributing to the excellent *ee*'s obtained with the peculiar dicarbonylic electrophiles **56** (Scheme 8).[44a]

In summary, transition-metal- and lanthanide- catalyzed Michael additions constitute useful alternatives to the more classical catalysts. High enantioselectivities have been secured in some cases. However, careful evaluation of all mechanistic possibilities should be performed for a better and successful use of such synthetic methods.

6. Papers which appeared during the refereeing process

During the refereeing process the following relevant papers have appeared. For the sake of completeness they will be listed here, but not discussed.
i. A review by Kanemasa and Ito on the double catalytic activation by nickel(II) and an amine.[69]
ii. Michael additions catalyzed by ruthenium hydrides.[70]
iii. Michael additions catalyzed by ruthenium amido complexes.[71]
iv. Cu(II) and Sc(III) in the interlayer space of montmorillonites as catalysts in carbon-carbon bond forming reactions.[72]
v. Highly enantioselective conjugate additions catalyzed by a (Salen)Al complex.[73]

Acknowledgments

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References

1. Jung, M.E. "Stabilized Nucleophiles with Electron Deficient Alkenes and Alkynes". In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Eds; Pergamon Press: Elmsford, NY, 1991; Vol. 4, Ch. 1.1.
2. Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Elmsford, NY, 1992.
3. Christoffers, J. *Eur. J. Org. Chem*. **1998**, 1259.
4. (a) Christoffers, J.; Baro, A. *Angew. Chem., Int. Ed*. **2003**, *42*, 1688. (b) Christoffers, J. *Chem. Eur. J*. **2003**, 4862. (c) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171.
5. (a) Shibasaki, M.; Yoshikawa, N. *Chem. Rev*. **2002**, *102*, 2187. (b) Matsunaga, S.; Ohshima, T.; Shibasaki, M. *Adv. Synth. Catal*. **2002**, *344*, 3.
6. Jha, S. C.; Joshi, N. N. *ARKIVOC* **2002**, (vii), 167.
7. Saegusa, T.; Ito, Y.; Tomitra, S.; Kinoshita, H. *Bull. Chem. Soc. Jpn*. **1972**, *45*, 496.
8. (a) Nelson, J. H.; Howells, P. N.; Landen, G. L.; DeLullo, G. C.; Henry, R. A. *Fundam. Res. Homogeneous Catal*. **1979**, *3*, 921. (b) Nelson, J. H.; Howells, P. N.; DeLullo, G. C.; Landen, G. L.; Henry, R. A. *J. Org. Chem*. **1980**, *45*, 1246.

9. Palombi, L.; Feroci, M.; Orsini, M.; Inegi, A. *Tetrahedron: Asymmetry* **2002**, *13*, 2311.
10. Bolm, C.; Legros, J.; Le Paih, J.; Zani, L. *Chem. Rev.* **2004**, *104*, 6217.
11. (a) Christoffers, J. *Tetrahedron Lett.* **1998**, *39*, 7083. (b) Christoffers, J. *J. Org. Chem.* **1998**, *63*, 4539. (c) Christoffers, J.; Mann, A. *Eur. J. Org. Chem.* **1999**, 2511. (d) Christoffers, J.; Oertling, H.; Leitner, M. *Synlett* **2000**, 349.
12. Chibiryaev, A. M.; De Kimpe, N.; Tkachev, A. V. *Tetrahedron Lett.* **2000**, *41*, 8011.
13. Shimizu, K.; Miyagi, M.; Kan-no, T.; Kodama, T.; Kitayama, Y. *Tetrahedron Lett.* **2003**, *44*, 7421.
14. Martínez, S.; Meseguer, M.; Casas, L.; Rodríguez, E.; Molins, E.; Moreno-Mañas, M.; Roig, A.; Sebastián, R. M.; Vallribera, A. *Tetrahedron* **2003**, *59*, 1553.
15. (a) Alvarez, S. G.; Hasegawa, S.; Hirano, M.; Komiya, S. *Tetrahedron Lett.* **1998**, *39*, 5209. (b) Hirano, M.; Takenaka, A.; Mizuho, Y.; Hiraoka, M; Komiya, S. *J. Chem. Soc., Dalton Trans.* **1999**, 3209. (c) Hirano, M.; Kiyota, S.; Imoto, M.; Komiya, S. *Chem. Commun.* **2000**, 1679.
16. (a) Naota, T.; Tannna, A.; Murahashi, S. *Chem. Commun.* **2001**, 63. (b) Murahashi, S.; Take, K.; Takaya, H. *Synlett* **2000**, 1016.
17. Picquet, M.; Bruneau, C.; Dixneuf, P. H. *Tetrahedron* **1999**, *55*, 3937.
18. (a) Watanabe, M.; Murata, K.; Ikariya, T. *J. Am. Chem. Soc.* **2003**, *125*, 7508. (b) Ikariya, T.; Wang, H.; Watanabe, M.; Murata, K. *J. Organometal. Chem.* **2004**, *689*, 1377. (c) Watanabe, M.; Ikagawa, A.; Wang, H.; Murata, K.; Ikariya, T. *J. Am. Chem. Soc.* **2004**, *126*, 11148.
19. Lumbierres, M.; Marchi, C.; Moreno-Mañas, M.; Sebastián, R. M.; Vallribera, A.; Lago, E.; Molins, E. *Eur. J. Org. Chem.* **2001**, 2321.
20. Brunner, H.; Krumey, H. *J. Mol. Catal. A* **1999**, *142*, 7.
21. End, N.; Macko, L.; Zehnder, M.; Pfaltz, A. *Chem. Eur. J.* **1998**, *4*, 818.
22. Inagaki, K.; Nozaki, K.; Takaya, H. *Synlett* **1997**, 119.
23. Sawamura, M.; Hamashima, H.; Ito, Y. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2559.
24. Suzuki, T.; Torii, T. *Tetrahedron: Asymmetry* **2001**, *12*, 1077.
25. Motoyama, Y.; Koga, Y.; Kobayashi, K.; Aoki, K.; Nishiyama, H. *Chem. Eur. J.* **2002**, *8*, 2968.
26. Hou, Z.; Koizumi, T.; Fujita, A.; Yamazaki, H.; Wakatsuki, Y. *J. Am. Chem. Soc.* **2001**, *123*, 5812.
27. Moreno-Mañas, M.; Marquet, J.; Vallribera, A. *Tetrahedron* **1996**, *52*, 3377.
28. (a) Clariana, J.; Gálvez, N.; Marchi, C.; Moreno-Mañas, M.; Vallribera, A.; Molins, E. *Tetrahedron* **1999**, *55*, 7331. (b) Marchi, C.; Trepat, E.; Moreno-Mañas, M.; Vallribera, A.; Molins, E. *Tetrahedron* **2002**, *58*, 5699.
29. Meseguer, M.; Moreno-Mañas, M.; Vallribera, A. *Tetrahedron Lett.* **2000**, *41*, 4093.
30. (a) Dell'Anna, M. M.; Gallo, V.; Mastrorilli, P.; Nobile, C. F.; Romanazzi, G.; Suranna, G. P. *Chem. Commun.* **2002**, 434. (b) Gallo, V.; Mastrorilli, P.; Nobile, C. F.; Romanazzi, G.; Suranna, G. P. *J. Chem. Soc., Dalton Trans.* **2002**, 4339.

31. Christoffers, J.; Rößler, U.; Werner, T. *Eur. J. Org. Chem*. **2000**, 701.
32. (a) Itoh, K.; Oderaotoshi, Y.; Kanemasa, S. *Tetrahedron: Asymmetry* **2003**, *14*, 635. (b) Itoh, K.; Kanemasa, S. *J. Am. Chem. Soc*. **2002**, *124*, 13394. (c) Itoh, K.; Kanemasa, S. *Tetrahedron Lett*. **2003**, *44*, 1799.
33. Blacker, A. J.; Clarke, M. L.; Loft, M. S.; Mahon, M. F.; Williams, J. M. J. *Organometallics* **1999**, *18*, 2867.
34. (a) Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc*. **2002**, *124*, 11240. (b) Hamashima, Y.; Takano, H.; Hotta, D.; Sodeoka, M. *Org. Lett*. **2003**, *5*, 3225.
35. (a) Stark, M. A.; Richards, C. J. *Tetrahedron Lett*. **1997**, *38*, 5881. (b) Stark, M. A.; Jones, G.; Richards, C. J. *Organometallics* **2000**, *19*, 1282. (c) Fossey, J. S.; Richards, C. J. *Organometallics* **2002**, *21*, 5259. (d) Fossey, J. S.; Richards, C. J. *Organometallics* **2004**, *23*, 367.
36. (a) Dijkstra, H. P.; Meijer, M. D.; Patel, J.; Kreiter, R.; van Klink, G. P. M.; Lutz, M.; Spek, A. L.; Canty, A. J.; van Koten, G. *Organometallics* **2001**, *20*, 3159. (b) Beletskaya, I. P.; Chuchuryukin, A. V.; van Koten, G.; Dijkstra, H. P.; van Klink, G. P. M.; Kashin, A. N.; Nefedov, S. E.; Eremenko, I. L. *Russ. J. Org. Chem*. **2003**, *39*, 1268. (c) Slagt, M. Q.; Stiriba, S.-E.; Klein Gebbink, J. M.; Kautz, H.; Frey, H.; van Koten, G. *Macromolecules* **2002**, *35*, 5734. (d) Stiriba, S.-E.; Slagt, M. Q.; Kautz, H.; Klein Gebbink, J. M.; Thomann, R.; Frey, H.; van Koten, G. *Chem. Eur. J*. **2004**, *10*, 1267.
37. Takenaka, K.; Uozumi, Y. *Org. Lett*. **2004**, *6*, 1833.
38. Mazet, C.; Gade, L. H. *Chem. Eur. J*. **2003**, *9*, 1759.
39. (a) Christoffers, J.; Mann, A. *Eur. J. Org. Chem*. **1999**, 1475. (b) Chistoffers, J.; Rößler, U. *Tetrahedron: Asymmetry* **1999**, *10*, 1207. (c) Christoffers, J.; Mann, A.; Pickardt, J. *Tetrahedron* **1999**, *55*, 5377.
40. (a) Christoffers, J.; Mann, A. *Angew. Chem., Int. Ed*. **2000**, *39*, 2752. (b) Christoffers, J.; Schuster, K. *Chirality* **2003**, *15*, 777. (c) Christoffers, J.; Mann, A. *Chem. Eur. J*. **2001**, *7*, 1014. (d) Christoffers, J.; Scharl, H. *Eur. J. Org. Chem*. **2002**, 1505.
41. (a) Christoffers, J.; Scharl, H.; Frey, W.; Baro A. *Org. Lett*. **2004**, *6*, 1171. (b) Christoffers, J.; Frey, W.; Scharl, H.; Baro, A. *Z. Naturforsch. B*. **2004**, *59*, 375.
42. Christoffers, J.; Kreidler, B.; Unger, S.; Frey, W. *Eur. J. Org. Chem*. **2003**, 2845.
43. Marigo, M.; Juhl, K.; Jørgensen, K. A. *Angew. Chem., Int. Ed*. **2003**, *42*, 1367.
44. (a) Halland, N.; Velgaard, T.; Jørgensen, K. A. *J. Org. Chem*. **2003**, *68*, 5067. (b) Juhl, K.; Jørgensen, K. A. *J. Am. Chem. Soc*. **2002**, *124*, 2420.
45. Ma, S.; Jiao, N.; Zheng, Z.; Ma, Z.; Lu, Z.; Ye, L.; Deng, Y.; Chen, G. *Org. Lett.* **2004**, *6*, 2193.
46. Comelles, J.; Moreno-Mañas, M.; Pérez, E.; Roglans, A.; Sebastián, R. M.; Vallribera, A. *J. Org. Chem*. **2004**, *69*, 6834.
47. Baruah, P. P.; Boruah, A.; Prajapati, D.; Sandhu, J. S. *Indian J. Chem. B* **1998**, *37(B)*, 425.
48. Kobayashi, S.; Kakumoto, K.; Mori, Y.; Manabe, K. *Israel J. Chem*. **2001**, *41*, 247.
49. Baruah, B.; Boruah, A.; Prajapati, D.; Sandhu, J. S. *Tetrahedron Lett*. **1997**, *38*, 1449.

50. (a) Yadav, J. S.; Geetha, V.; Subba Reddy, B. V. *Synth. Commun.* **2002**, *32*, 3519. (b) Yadav, J. S.; Subba Reddy, B. V.; Venugopal, Ch; Padmavani, B. *Tetrahedron Lett.* **2004**, *45*, 7507.
51. Hidehiko, K.; Masahiro, S.; Nagata, C. *Nippon Kagaku Kaishi* **1999**, 145; *Chem. Abstr.* 130:267140.
52. Mikami, K.; Terada, M.; Matsuzawa, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3554.
53. Bonadies, F.; Lattanzi, A.; Orelli, L. R.; Pesci, S.; Scettri, A. *Tetrahedron Lett.* **1993**, *34*, 7649.
54. Mori, Y.; Kakumoto, K.; Manabe, K.; Kobayashi, S. *Tetrahedron Lett.* **2000**, *41*, 3107.
55. (a) Nakajima, M.; Yamaguchi, Y.; Hashimoto, S. *Chem. Commun.* **2001**, 1596. (b) Nakajima, M.; Yamamoto, S.; Yamaguchi, Y.; Nakamura, S.; Hashimoto, S. *Tetrahedron* **2003**, *59*, 7307.
56. Kawabata, T.; Mizugaki, T.; Evitan, K.; Kaneda, K. *J. Am. Chem. Soc.* **2003**, *125*, 10486.
57. Saiki, T.; Aoyama, Y. *Chem. Lett.* **1999**, 797.
58. (a) Kim, Y. S.; Matsunaga, S.; Das, J.; Sekine, A.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6506. (b) Matsunaga, S.; Ohshima, T.; Shibasaki, M. *Adv. Synth. Catal.* **2002**, *344*, 3. (c) Majima, K.; Takita, R.; Okada, A.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 15837. (d) Ohshima, T.; Youjun, X.; Kim, Y. S.; Matsunaga, S.; Ohori, K.; Shibasaki, M. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **2000**, *42nd*, 145; *Chem. Abstr.* 134:295978.
59. Bartoli, G.; Marcantoni, E.; Sambri, L. *Synlett* **2003**, 2101.
60. Bartoli, G.; Bosco, M.; Bellucci, M. C.; Marcantoni, E.; Sambri, L.; Torregiani, E. *Eur. J. Org. Chem.* **1999**, 617.
61. Boruah, A.; Baruah, M.; Prajapati, D.; Sandhu, J. S. *Synth. Commun.* **1998**, *28*, 653.
62. (a) Liu, Y.; Zhang, Y.; Li, Z. *J. Indian Chem. Soc.* **2002**, *79*, 433. (b) Ma, Y.; Zhang, Y. *Synth. Commun.* **2002**, *32*, 819. (c) Chen, X.; Bao, W.; Zhang, Y. *Chin. Chem. Lett.* **2000**, *11*, 483; *Chem. Abstr.* 133, 252035.
63. De Rosa, M.; Palombi, L.; Acocella, M. R.; Fruilo, M.; Villano, R.; Soriente, A.; Scettri, A. *Chirality* **2003**, *15*, 579.
64. (a) Kotsuki, H.; Arimura, K.; Ohishi, T.; Maruzasa, R. *J. Org. Chem.* **1999**, *64*, 3770. (b) Kotsuki, H.; Arimura, K. *Tetrahedron Lett.* **1997**, *38*, 7583.
65. Pelzer, S.; Kauf, T.; van Wüllen, C.; Christoffers, J. *J. Organometal. Chem.* **2003**, *684*, 308.
66. Trage, C.; Schröder, D.; Schwarz, H. *Chem. Eur. J.* **2005**, *11*, 619.
67. Kobayashi, S.; Nagayama, S.; Busujima, T. *J. Am. Chem. Soc.* **1998**, *120*, 8287.
68. Wabnitz, T. C.; Yu, J.-Q.; Spencer, J. B. *Chem. Eur. J.* **2004**, *10*, 484.
69. Kanemasa, S.; Ito, K. *Eur. J. Org. Chem.* **2004**, 4741.
70. Guo, R.; Morris, R. H.; Song, D. *J. Am. Chem. Soc.* **2005**, *127*, 516.
71. Wang, H.; Watanabe, M.; Ikariya, T. *Tetrahedron Lett.* **2005**, *46*, 963.
72. Kawabata, T.; Kato, M.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *Chem. Eur. J.* **2005**, *11*, 288.
73. Taylor, M. S.; Zalatan, D. N.; Lerchner, A. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 1313.

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