



HAL
open science

Enantioselective Aluminum-catalyzed Transformations using Chiral Organic Ligands. An Update

Hélène Pellissier

► **To cite this version:**

Hélène Pellissier. Enantioselective Aluminum-catalyzed Transformations using Chiral Organic Ligands. An Update. *Current Organic Chemistry*, 2025, 29, <10.2174/0113852728370767250309180907>. <hal-05055743>

HAL Id: hal-05055743

<https://hal.science/hal-05055743v1>

Submitted on 5 May 2025

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



HAL Authorization

Enantioselective Aluminum-catalyzed Transformations using Chiral Organic Ligands. An Update

Hélène Pellissier*

Aix Marseille Univ, CNRS, Centrale Med, iSm2, Marseille, France

Fax: +33 4 13 94 56 41; e-mail: h.pellissier@univ-amu.fr

Abstract: Aluminum is the most abundant metal in the Earth's crust and is also the principal constituent of many common minerals. Taking advantages of its higher abundance and both lower costs and toxicity in comparison with more traditional transition metals, this main group metal has emerged as a green metal of high potential and utility in organic synthesis. While many racemic aluminum catalysts have been early applied as Lewis acids to promote various reactions, such as Friedel-Crafts acylations, Alder-ene reactions and polymerizations, chiral aluminum counterparts have been developed only since 1990s in asymmetric catalysis. Indeed, the possibility of tuning the Lewis acidity of aluminum by making use of appropriate chiral ligands, allows to control the stereoselectivity in a wide diversity of catalytic enantioselective reactions. For example, various types of ligands have been chelated to aluminum, such as salens, BINOL and VANOL derivatives, TADDOL-derived ligands, cinchona alkaloids, and *N,N'*-dioxides. In the last decade, a wide variety of highly enantioselective aluminum-catalyzed transformations have been developed, spanning from basic reactions, such as cyanations of carbonyl compounds, aldol reactions, reductions, cycloadditions, cyclizations, α -alkylations of aldehydes, Michael additions, acyloin rearrangements, copolymerizations etc., to more challenging and modern processes, such as domino and tandem reactions. The goal of this review is to collect the recent developments in enantioselective aluminum-catalyzed reactions of all types published since the beginning of 2015. It shows that asymmetric aluminum catalysis, that suits the growing demand for greener processes, offers a real opportunity to replace toxic and expensive metals soon.

Keywords: Asymmetric aluminum catalysis; enantioselective reactions; metal catalysis; chirality; asymmetric catalysis

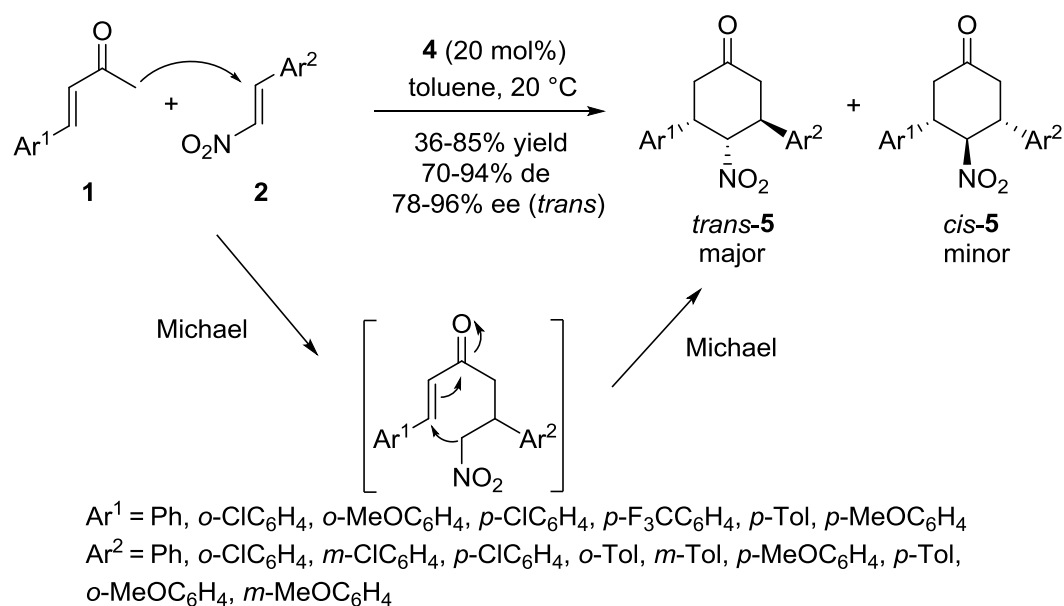
1. INTRODUCTION

Aluminum is the most abundant metal in the Earth's crust and is also the principal constituent of many common minerals. Taking advantages of its higher abundance and lower costs and toxicity in comparison with more traditional transition metals [1], this main group metal is becoming a green opportunity in organic synthesis. Aluminum is almost present in the +3 oxidation state in aluminum complexes. While many racemic aluminum catalysts have been early applied as Lewis acids to promote various reactions, such as Friedel-Crafts acylations, Alder-ene reactions and polymerizations, chiral aluminum counterparts have been developed only since 1990s in asymmetric catalysis [2]. Indeed, the possibility of tuning the Lewis acidity of aluminum by making use of appropriate chiral ligands, allows to control the stereoselectivity in a wide diversity of catalytic enantioselective reactions. A variety of ligands have been complexed to aluminum, such as salens, BINOL and VANOL derivatives, TADDOL-derived ligands [3], cinchona alkaloids, and *N,N'*-dioxides. Especially in the last decade, enantioselective aluminum-catalyzed transformations of high efficiency have been developed, including aldol condensations, cyanations of carbonyl compounds, reductions, cyclizations, cycloadditions, α -alkylations of aldehydes, acyloin rearrangements, Michael additions, copolymerizations, and domino/tandem reactions. This review intends to update the field of enantioselective aluminum-catalyzed reactions published since 2015, because the last report in this subject dated from 2016 with a book chapter published by Feng and Xie including references up to 2014 [4]. The same year, a review focusing on enantioselective main group catalysis was reported by Melen and Wilkins albeit it included none reference \geq 2015 dealing with asymmetric aluminum-catalyzed transformations [5]. More recently in 2019, Gualandi and Cozzi reviewed aluminum (salen) complexes in stereoselective catalysis but only four references \geq 2015 concerning applications of this special type of metal catalysts were included [6]. In 2022, Ye and Luan published a report on bifunctional ligand-ligated Ni–Al bimetallic catalysis applied to C–H and C–C bond activation including only six references \geq 2015 focusing on

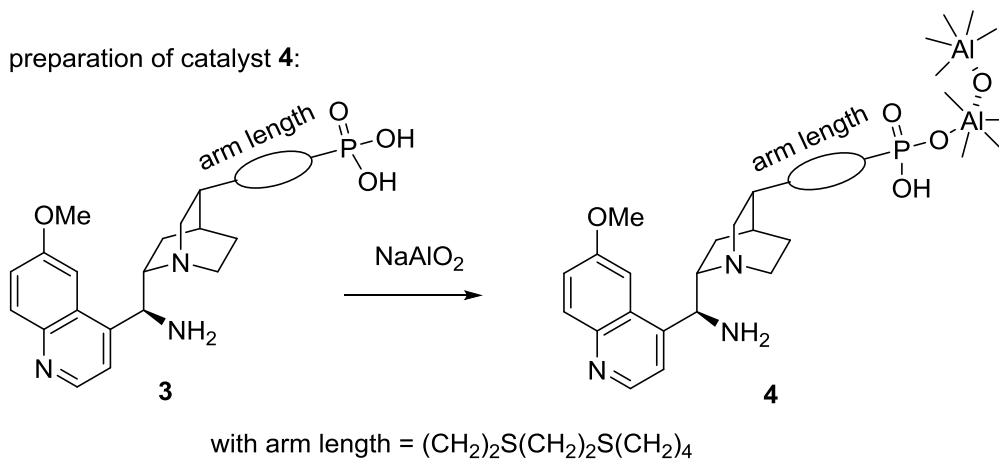
asymmetric reactions [7]. Moreover, different reviews dealing with organoaluminum reagents were previously published [8]. In 2024, a mini-review focusing on asymmetric catalysis using general p-block elements was published by Melen et al., including only six references \geq 2015 concerning aluminum [9]. This review is divided into seven sections, focusing successively on enantioselective aluminum-catalyzed domino and tandem reactions, cyanations of carbonyl compounds, kinetic resolutions, desymmetrizations and deracemizations, aldol reactions, reductions of ketones, cyclizations, and miscellaneous reactions.

2. DOMINO AND TANDEM REACTIONS

One-step domino reactions permit the direct synthesis of complex molecules from simple starting materials, avoiding the costly isolation and purification of intermediates [10]. Combining asymmetric aluminum catalysis with the concept of domino/tandem reactions allows the synthesis of many types of chiral complex products to be simply achieved with generally high enantioselectivities. The blooming of these reactions has already permitted the synthesis of a wide diversity of cyclic as well as acyclic complex chiral molecules. The first and still rare examples of enantioselective aluminum-catalyzed domino processes were described by Zhu et al. in 2007 [11]. Therefore, these authors reported the use of a chiral aluminum salen complex to promote an asymmetric domino aldol/cyclization reaction of α -isocyanoacetamides with aldehydes to give the corresponding chiral 5-aminooxazoles with enantioselectivities of up to 80% ee. In 2008, the same catalyst was applied to develop an enantioselective three-component Passerini reaction between an aldehyde, a carboxylic acid and an isocyanide to afford an enantiopure α -acyloxyamide (>99% ee) [12]. The same year, a closely related aluminum complex was found capable of promoting another asymmetric three-component reaction between aldehydes, isocyanides and hydrazoic acid, resulting in the formation of the corresponding chiral (hydroxyalkyl)tetrazoles with up to 97% ee [13]. More recently in 2017, Ma et al. developed the synthesis of chiral cinchona alkaloid-tethered aluminum phosphonate complexes to be applied as heterogeneous cooperative catalysts in different types of asymmetric transformations [14]. Among them are enantioselective domino double Michael reactions of α,β -unsaturated ketones **1** with aromatic nitroalkenes **2** performed in toluene at 20 °C (Scheme 1). The best results were achieved when using 20 mol% of catalyst **3** which was easily prepared by precipitation of the corresponding chiral phosphonate **4** with sodium aluminate. This dual cooperative catalyst allowed the synthesis of a variety of chiral functionalized cyclohexanones **5** to be achieved with moderate to high yields (36-85%) as major *trans*-diastereomers in good to high diastereoselectivities (70-94% de) and uniformly high enantioselectivities (78-96% ee). It must be noted that the catalyst could be recovered through centrifugation and reused without significant loss of catalytic activity for up to five runs. While generally the immobilization of organocatalyst into a solid is limited to a single organocatalyst, this work proposed the first in situ generation of a novel heterogeneous cooperative catalyst tethered on an aluminum phosphonate. The future application of this new catalyst to more cooperatively organocatalytic reactions will provide access to other complex chiral molecules with multiple stereogenic centers through a green manner.

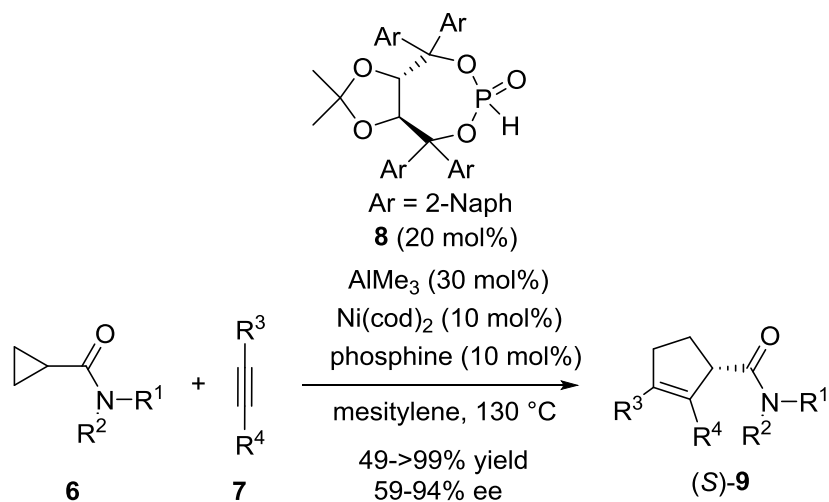


preparation of catalyst 4:



Scheme 1. Domino double Michael reaction of α,β -unsaturated ketones with aromatic nitroalkenes.

The same year, an enantioselective formal [3+2] cycloaddition between three-membered carboxamides **6** and alkynes **7** was described for the first time by Ye et al. (Scheme 2) [15]. It involved a dual metal catalyst system constituted by 10 mol% of $\text{Ni}(\text{cod})_2$, 30 mol% of AlMe_3 , and 20 mol% of chiral ligand **8** derived from TADDOL. When the process was carried out at 130 °C in mesitylene in the presence of 10 mol% of a tertiary phosphine (PR_3) as an additive, it resulted in the formation of chiral cyclopentenyl derivatives (*S*)-**9** with 49- >99% yields and 59-94% ee. Generally, good yields (60-99%) and high enantioselectivities (86-94% ee) were obtained in the reaction of symmetrical aromatic alkynes ($\text{R}^3 = \text{R}^4 = (\text{hetero})\text{aryl}$) while aliphatic alkynes reacted with both lower yields (43-63%) and enantioselectivities (59-77% ee). To explain the results, the authors proposed the mechanism depicted in Scheme 2, beginning with the formation of intermediate **A** from the reaction between the ligand, $\text{Ni}(\text{cod})_2$ and AlMe_3 . Then, intermediate **A** coordinated with the cyclopropyl carboxamide to generate intermediate **B**. A subsequent tertiary phosphine-assisted oxidative addition of nickel to the C-C bond of the cyclopropane afforded four-membered intermediate **C**. The latter further inserted into the alkyne moiety to give six-membered nickel intermediate **D**. A final reductive elimination delivered the cyclopentenyl carboxamide and regenerated the catalytic species. This novel methodology allowed for the first time the elusive challenge that is the cycloaddition of unreactive cyclopropyl carboxamides with alkynes. This resulted in the preparation of synthetically useful cyclopentenyl chiral carboxamides in up to 99% yield and 94% ee.



phosphine = $\text{P}(\text{o-Tol})_3$, Cy_2PTipp or Cy_2PPh
 Tipp = (2,4,6-triisopropyl)phenyl

$\text{R}^1, \text{R}^2 = (\text{CH}_2)_5, (\text{CH}_2)_2\text{O}(\text{CH}_2)_2$

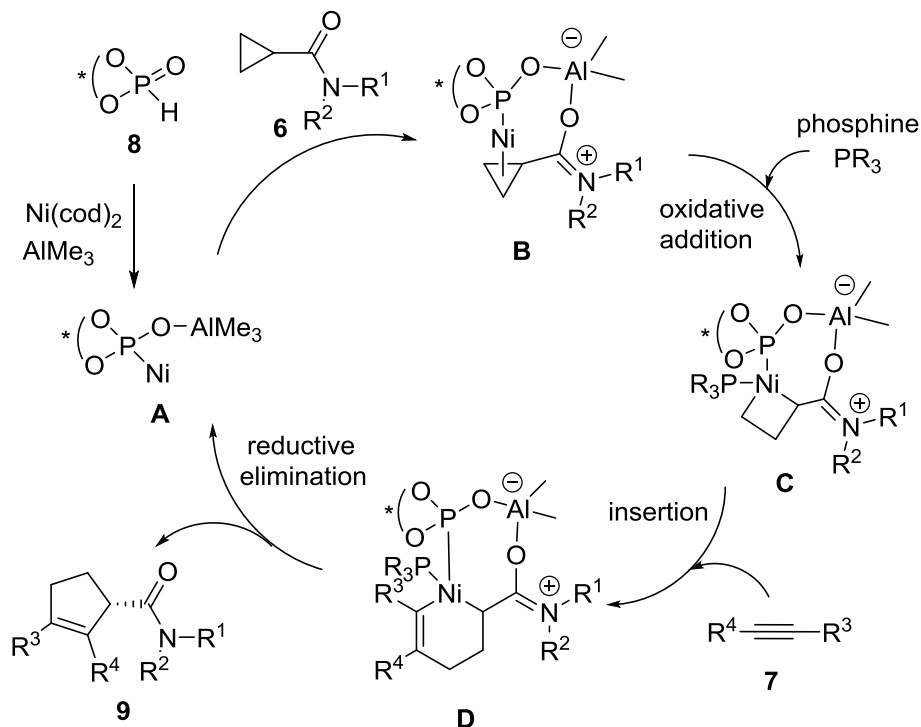
$\text{R}^1 = \text{Me}$

$\text{R}^2 = \text{Ph}$

$\text{R}^3 = \text{Ph}, p\text{-Tol}, p\text{-MeOC}_6\text{H}_4, o\text{-MeOC}_6\text{H}_4, m\text{-MeOC}_6\text{H}_4, p\text{-F}_3\text{COC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, 3\text{-thienyl}, o\text{-Tol}, m\text{-Tol}, p\text{-EtC}_6\text{H}_4, p\text{-t-BuC}_6\text{H}_4, n\text{-Bu}$

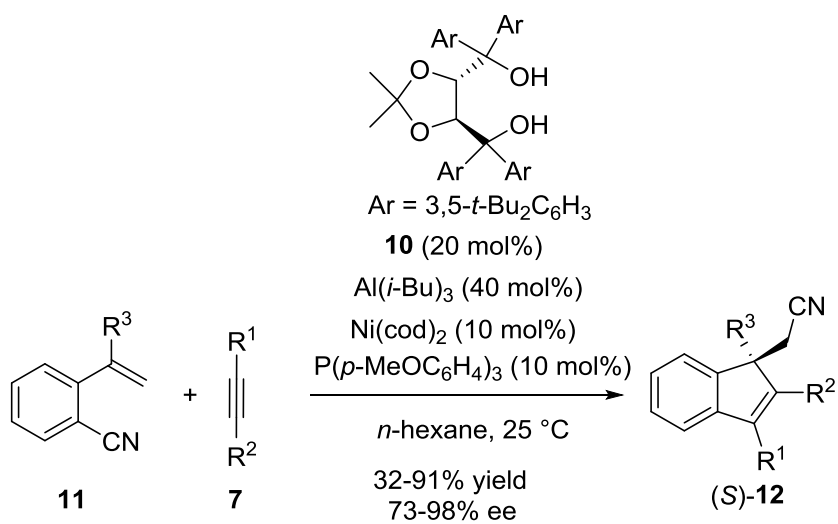
$\text{R}^4 = \text{Ph}, p\text{-Tol}, p\text{-MeOC}_6\text{H}_4, o\text{-MeOC}_6\text{H}_4, m\text{-MeOC}_6\text{H}_4, p\text{-F}_3\text{COC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, 3\text{-thienyl}, o\text{-Tol}, m\text{-Tol}, p\text{-EtC}_6\text{H}_4, p\text{-t-BuC}_6\text{H}_4, n\text{-Bu}, \text{TMS}$

proposed mechanism:



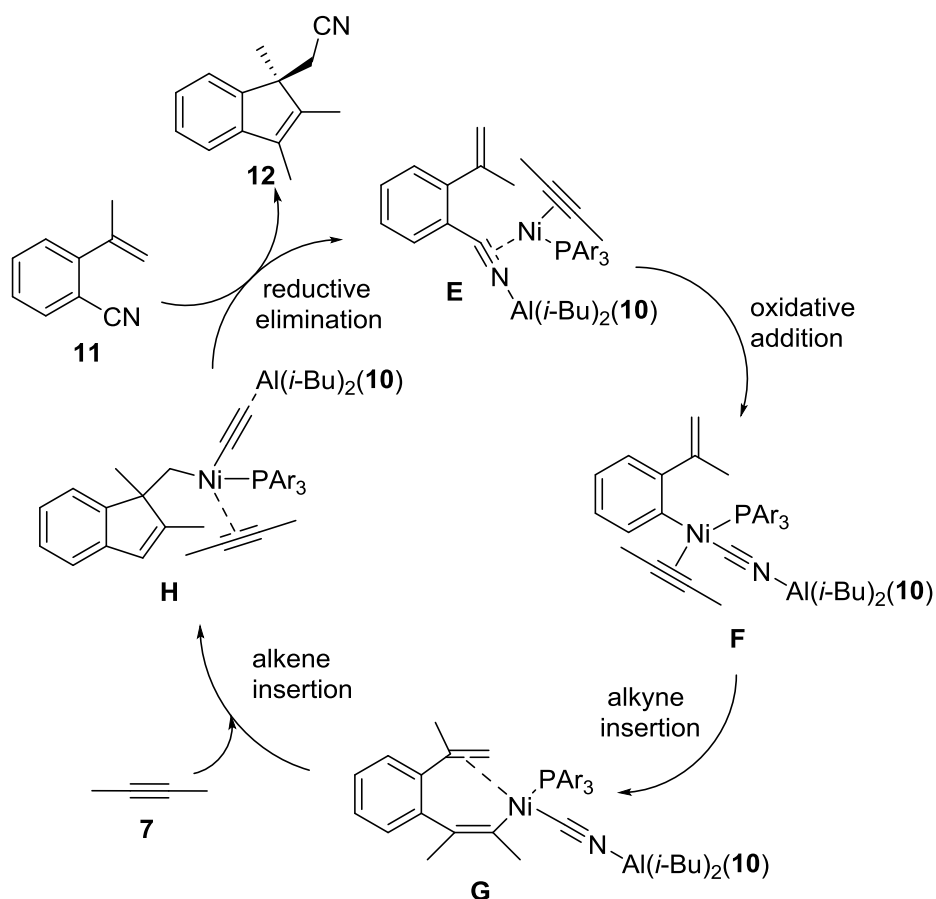
Scheme 2. Formal [3+2] cycloaddition of three-membered carboxamides with alkynes.

In 2020, Ye and Peng developed a novel and rare example of asymmetric domino reaction of aryl nitriles with alkynes catalyzed by a bimetallic Al/Ni complex (Scheme 3) [16]. The process involved as catalyst system a mixture of 10 mol% of Ni(cod)₂, 40 mol% of Al(*i*-Bu)₃, and 20 mol% of chiral ligand **10** derived from TADDOL. The latter promoted at 25 °C in hexane as the solvent the reaction of aryl nitriles **11** with alkynes **7** to give the corresponding chiral indenenes (*S*)-**12** exhibiting a quaternary stereocenter with 32-91% yields and 73-98% ee. The reaction required the use of 20 mol% of an achiral tertiary phosphine, such as (*p*-MeOC₆H₄)₃P, as an additive. The phenyl ring of aryl nitriles could bear electron-donating as well as -neutral substituents, providing both good yields (62-90%) and ee values (86-95% ee) while that of electron-withdrawing substituents decreased the enantioselectivity of the reaction (73-90% ee). Although the presence of bulky groups, such as *t*-butyl or an aryl group at the 2-position of the alkene (R³) were not tolerated, that of an ethyl group or functionalized linear alkyl chains were compatible, affording the desired products with 93-98% ee. Along with a series of symmetrical alkyl alkynes found compatible, a nonsymmetrical aryl alkyl alkyne (R¹ = Ph, R² = *n*-Bu) produced the desired product as a single product with 48% yield and 87% ee. To explain the results, the authors proposed the mechanism depicted in Scheme 3 in which first intermediate **E** was generated from the coordination of the nickel to the two triple bonds of the nitrile and the alkyne, concomitantly with the interaction between the aluminum species and the nitrogen of the nitrile group. Then, oxidative addition of the C–CN bond to Ni(0), assisted by coordination of the nitrile group with Al, generated Ni(II) intermediate **F**. The latter underwent alkyne insertion to afford intermediate **G**, with the olefin coordinated to a Ni(II) center. A subsequent insertion of the alkene resulted in the formation of intermediate **H** which was further submitted to reductive elimination in the presence of another alkyne, leading to the final domino product and regenerated catalysts. This novel methodology using an inexpensive achiral phosphine presented the advantage to be a rare route to chiral indenenes bearing all-carbon quaternary stereocenters which are important structural motifs present in bioactive products. While many racemic synthetic methods to prepare racemic indenenes exist, enantioselective versions remain scarce because the rigid ring and the sterically hindered carbon center render asymmetric control challenging.



$\text{R}^1 = \text{Ph}, n\text{-Hex}, n\text{-Bu}, \text{Et}, n\text{-Pr}$
 $\text{R}^2 = n\text{-Bu}, n\text{-Pr}, \text{Et}, n\text{-Hex}$
 $\text{R}^3 = \text{Me}, \text{MeO}(\text{CH}_2)_2, \text{BnO}(\text{CH}_2)_2, \text{Et}$

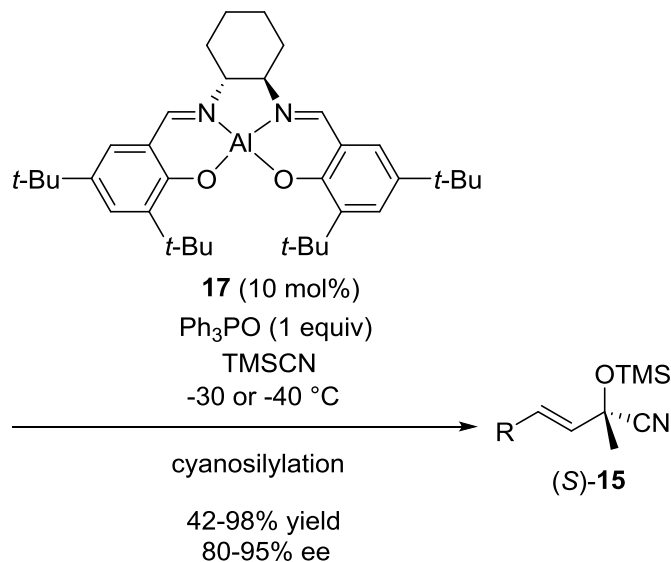
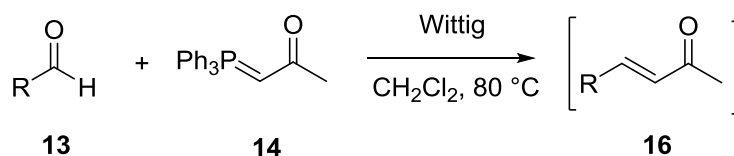
proposed mechanism ($\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{Me}, \text{Ar} = p\text{-MeOC}_6\text{H}_4$):



Scheme 3. Domino reaction of aryl nitriles with alkynes.

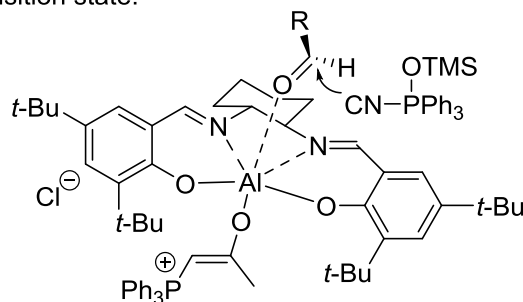
Tandem processes, occurring under not strictly the same reaction conditions in contrast with domino reactions, also constitute powerful one-pot methodologies to easily prepare very complex molecules [17]. In

2016, Zhou et al. disclosed an asymmetric aluminum-catalyzed tandem Wittig/cyanosilylation reaction of aldehydes **13** with phosphorane **14** and TMSCN, resulting in the formation of a wide range of cyanohydrins (*S*)-**15** bearing an alkene, a conjugated diene or an enyne group (Scheme 4) [18]. The first step of the sequence dealt with a Wittig reaction between aldehydes **13** and phosphorane **14** performed in dichloromethane at 80 °C, providing the corresponding α,β -unsaturated ketones **16**. The latter subsequently underwent at -30 °C an enantioselective aluminum-catalyzed cyanosilylation in the presence of TMSCN. This second step was promoted by 10 mol% of chiral salen aluminum catalyst **17** and one equivalent of Ph₃PO as a stoichiometric cocatalyst. Actually as detailed in Scheme 4, phosphorane **14** was employed as substrate in the first step of the sequence but also played the role of activating the aluminum catalyst while Ph₃PO activated TMSCN. An orthogonal activation of both the aluminum catalyst and TMSCN by the phosphorane and Ph₃PO, respectively, is illustrated in the transition state depicted in Scheme 4. This mechanism was supported by NMR analyses and DFT calculations. Moreover, the formation of charged complexes through the activation of the chiral catalyst by the phosphorane was confirmed by electrical conductivity experiments. The tandem reaction resulted in the obtention of a variety of chiral alkenes, dienes, trienes and enynes **15** with moderate to quantitative yields (42-98%) and high enantioselectivities (80-95% ee). Chiral dienes exhibiting two, three or four substituents on the alkene moiety were generated as well as optically active conjugated trienes and enynes with either an aryl or alkyl substituent. Moreover, non-conjugated aliphatic aldehydes (R = alkyl) were also compatible, providing the corresponding chiral cyanohydrins with 90-95% ee albeit combined with lower yields (56-75%). The authors demonstrated the utility of this novel asymmetric tandem cascade by converting one product into the natural antibiotic fostriecin.



R = (*E*)-PhCH=CH, (*E*)-*m*-TolCH=CH, (*E*)-*o*-FC₆H₄CH=CH, (*E*)-*m*-FC₆H₄CH=CH, (*E*)-*p*-ClC₆H₄CH=CH, (*E*)-2-thienylCH=CH, (*E*)-PhCH=CMe, (*E*)-PhCH=CCl, (*E*)-BnCH₂CH=CH, (*E*)-BnOCH₂CH=CH, (*E*)-PhC(Me)=CH, (*E*)-PhCH=CBr, (*E*)-PhC(Cl)=CH, (*E*)-Ph(CH=CH)₂, (*E*)-*n*-PentCH=CH, PhC≡C, BnOC≡C, (*E*)-PhC CCH=CH, BnOCH₂, *n*-Pent, *n*-Pr, *n*-Bu, BnCH₂, Bn(CH₂)₂

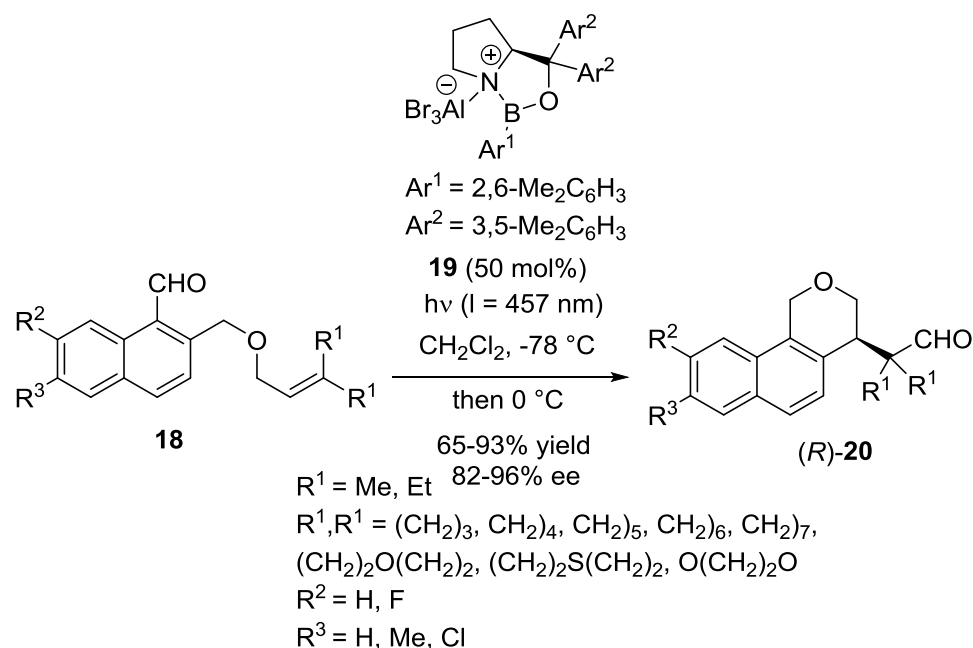
proposed transition state:



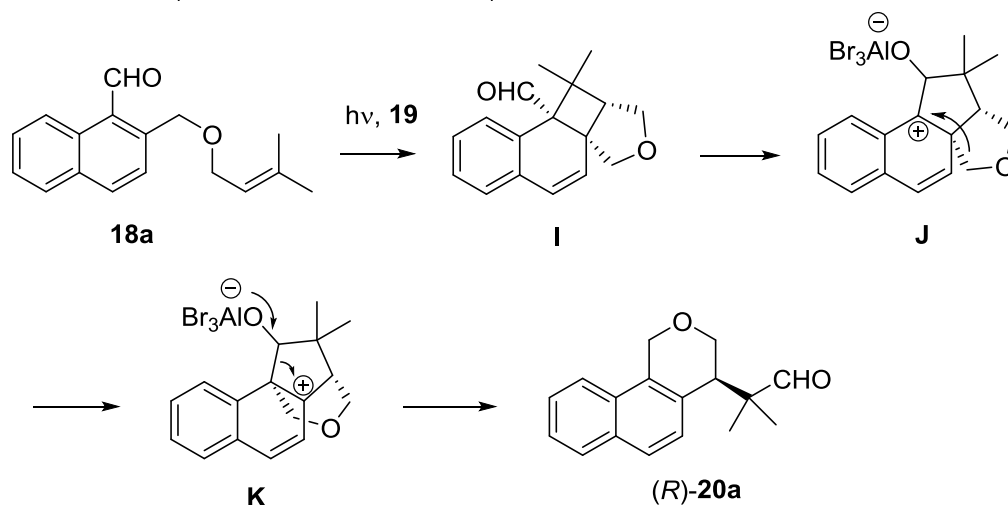
Scheme 4. Tandem Wittig/cyanosilylation reaction of a phosphorane, aldehydes and TMSCN.

Despite their obvious utility, enantioselective versions of cascade reactions including a photochemical step remain rare. To fill this gap, Bach et al. developed in 2022 an enantioselective tandem photocycloaddition/rearrangement reaction of 1-naphthaldehydes bearing a tethered allylic alcohol **18** promoted by chiral 1,3,2-oxazaborolidine aluminum catalyst **19** [19]. The cascade was initiated at -78 °C in dichloromethane by irradiation with visible light ($\lambda = 457$ nm) under catalysis with 50 mol% of complex **19**. Then, the reaction mixture was warmed to 0 °C after the irradiation to lead through rearrangement to the corresponding polycyclic benzoisochromenes (*R*)-**20** with 65-93% yields and 82-96% ee, as illustrated in Scheme 5. The authors demonstrated that the photocycloaddition step governed the enantioselectivity of the tandem reaction, giving chiral four-membered intermediate **I**. The latter species coordinated to aluminum center through its carbonyl group, undergoing a 1,2-alkyl shift which generated intermediate **J**. Then, the latter was submitted to a second migration to give intermediate **K**. Subsequent elimination of the Lewis acid and ring

scission regenerated the aldehyde moiety, resulting in aromatization which delivered the final product. In addition to constitute a rare example of asymmetric tandem reactions including a photochemical step, this novel transformation enabled the formation of structurally unique polycyclic products.



mechanism (with $\text{R}^1 = \text{Me}, \text{R}^2 = \text{R}^3 = \text{H}$):

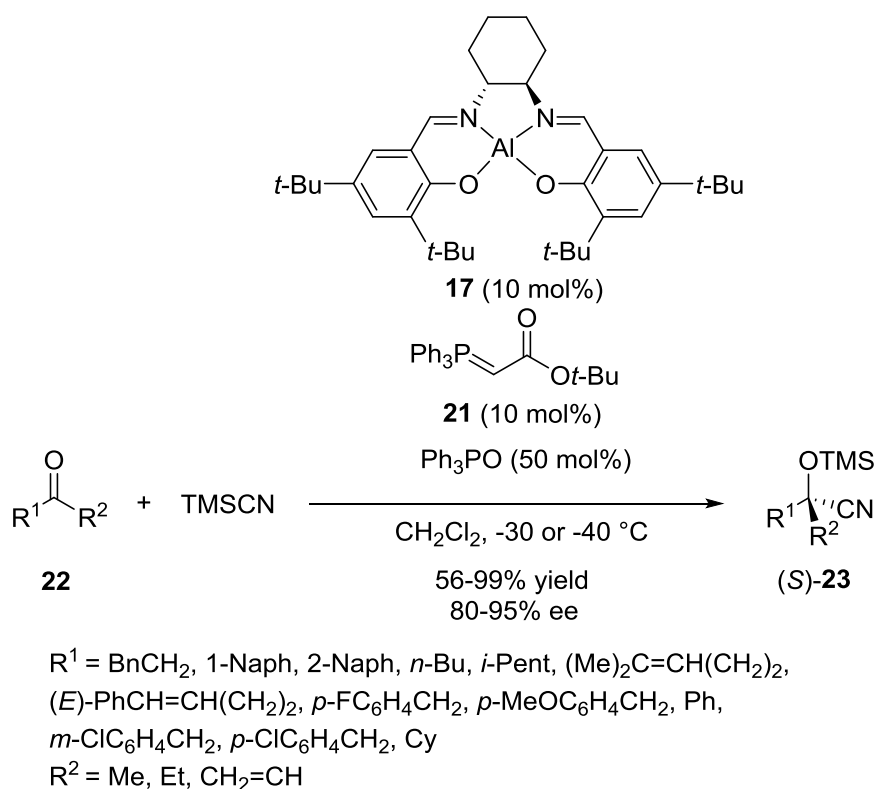


Scheme 5. Tandem photocycloaddition/rearrangement reaction of 1-naphthaldehydes.

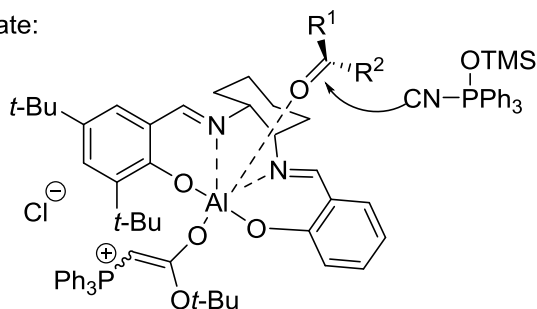
3. CYANATIONS OF CARBONYL COMPOUNDS

The cyanation reaction presents the synthetic advantage to form a new C–C bond, novel functionalities (alcohol and cyanide) with concomitant creation of a stereogenic center in a single transformation. Lewis acid catalysts have been widely employed to catalyze these reactions, affording cyanohydrins which are key intermediates in organic synthesis [20]. Among these catalysts, a chiral aluminum salen complex was applied for the first time by Jacobsen and Sigman in 1998 to promote the cyanation of carbonyl compounds derivatives, such as imines, with enantioselectivities of up to 95% ee [21]. Ever since, many efforts have been accomplished in the field of cyanation of ketones and derivatives [20d,22]. However, while a number of chiral catalysts have been demonstrated to be efficient in highly enantioselective cyanosilylations of alkyl aryl ketones, the

involvement of dialkyl ketones still remains challenging. In this context, Zhou et al. developed in 2016 the application of a catalyst system, constituted by a combination of salen aluminum complex **17**, triphenylphosphine oxide, and phosphorane **21**, to promote asymmetric cyanosilylation of dialkyl and alkyl aryl ketones **22** (Scheme 6) [18]. Indeed, in the presence of a mixture of 10 mol% of chiral aluminum salen catalyst **17**, 50 mol% of triphenylphosphine oxide, and 10 mol% of phosphorane **21** in dichloromethane, the asymmetric cyanosilylation of a range of simple ketones **22** performed at -30 or -40 °C was achieved, affording cyanohydrins (*S*)-**23** with 56-99% yields and 80-95% ee. Especially, the reaction of dialkyl ketones afforded the corresponding products with both high yields (85-97%) and enantioselectivities (80-95% ee). The lowest ee value (80% ee) was obtained for cyclohexyl vinyl ketone ($R^1 = \text{vinyl}$, $R^2 = \text{Cy}$) while other aliphatic ketones provided 89-95% ee. Furthermore, alkyl aryl ketones were also compatible, yielding the desired cyanohydrins with moderate to quantitative yields (56-99%) and high enantioselectivities (89-92% ee). As illustrated by the transition state depicted in Scheme 6, sterically hindered phosphorane **21** activated the chiral aluminum salen complex to enhance its electrophilicity while TMSCN was activated by Ph_3PO .



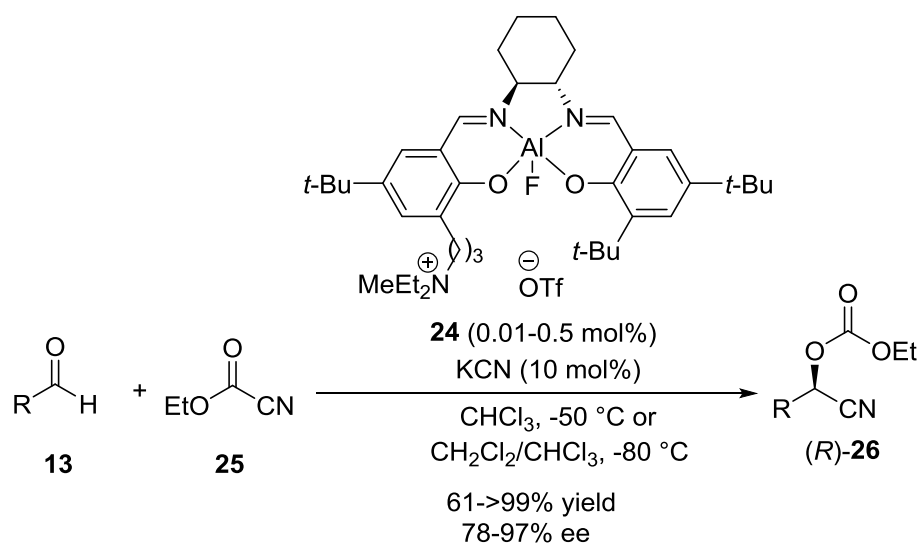
proposed transition state:



Scheme 6. Cyanosilylation of dialkyl and alkyl aryl ketones with TMSCN.

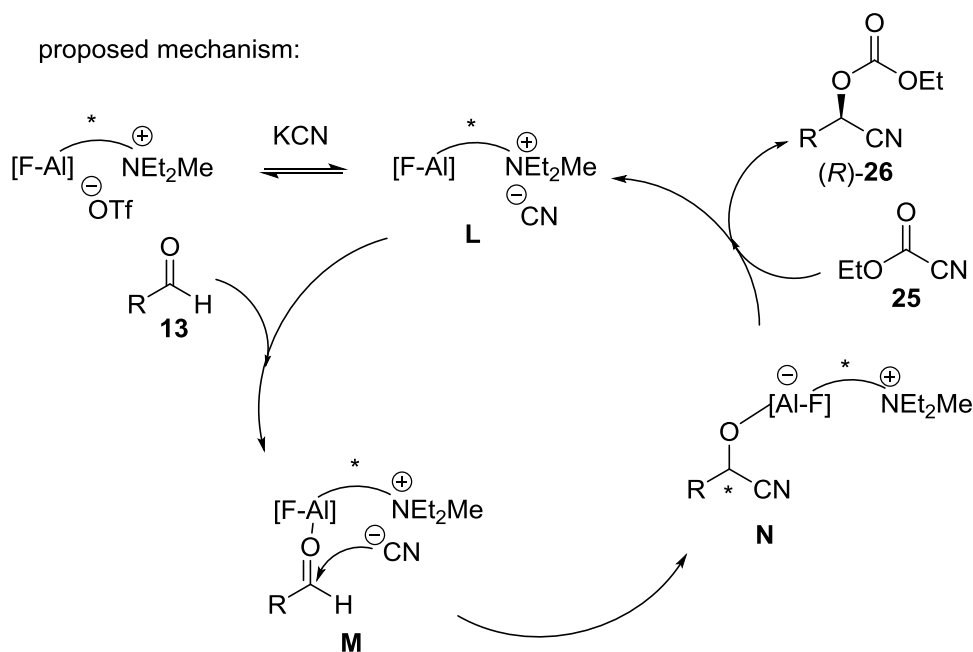
In 2017, Peters et al. demonstrated that aluminum fluoride salen complex **24** exhibiting an appended ammonium salt provided a remarkable catalytic activity in the asymmetric carboxycyanation of aldehydes [23]. Indeed, this stable complex employed in most cases at as low as 0.01 mol% of catalyst loading was found capable to promote the asymmetric carboxycyanation of many types of aldehydes **13** with ethyl cyanofornate **25** performed in chloroform as solvent in the presence of KCN as an additive to give the corresponding cyanohydrins (*R*)-**26** in both good to excellent yields (61->99%) and enantioselectivities (78-97% ee), as

illustrated in Scheme 7. A range of variously substituted aromatic aldehydes were compatible (61->99% yield, 80-93% ee) as well as an heteroaromatic substrate (R = 2-furyl) which afforded the corresponding product with 98% yield and 82% ee. Moreover, the reaction of α,β -unsaturated aldehydes provided both excellent yields (90->99%) and ee values (93-96% ee). Enolizable substrates, such as propanal and dihydrocinnamaldehyde, were also compatible with 99% yield and 81-90% ee. Even a bulky aliphatic substrate, such as pivaldehyde (R = *t*-Bu), reacted with quantitative yield (99%) albeit with a decreased enantioselectivity (78% ee). The authors showed that catalyst loading as low as 0.01 mol% still allowed very high ee values and quantitative yields to be achieved (R = (*E*)-MeCH=CH: 98% yield, 93% ee). Turnover numbers of up to around 10^4 were achieved, demonstrating the exceptional activity of catalyst **24**. A cooperative catalysis between the aluminum Lewis acid and the internal ammonium salt moiety was proposed by the authors in the mechanism depicted in Scheme 7. Addition of KCN to the original catalyst **24** led to complex **L** which activated aldehyde **13** through coordination to the aluminum center in intermediate **M**. This facilitated the 1,2-addition of the closely bound cyanide to the aldehyde, affording intermediate **N**. Then, the latter led to the final product and regenerated catalyst through carboxylation with ethyl cyanoformate **25**.



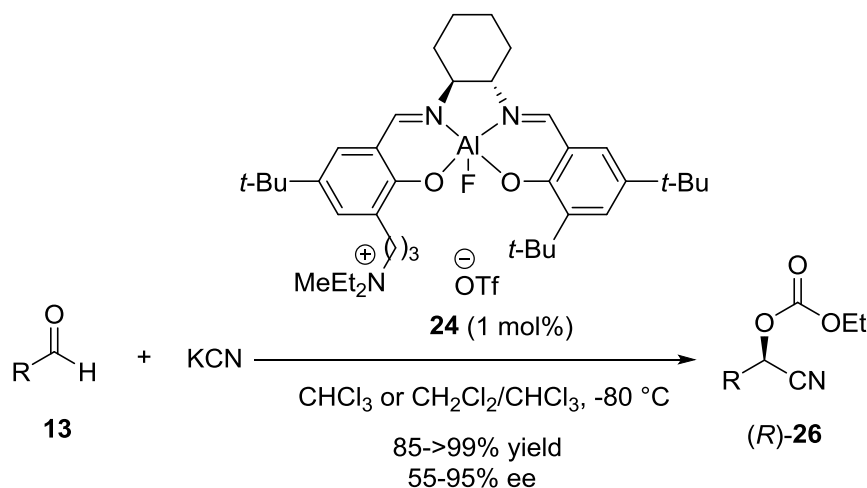
R = 2-Naph, 6-MeO-2-Naph, Ph, *p*-Tol, *m*-Tol, *o*-Tol, *p*-MeOC₆H₄, *m*-MeOC₆H₄, *o*-MeOC₆H₄, 3,4-Me₂C₆H₃, *p*-ClC₆H₄, *p*-FC₆H₄, *m*-MeO₂CC₆H₄, 2-furyl, (*E*)-PhCH=CH, (*E*)-*p*-MeOC₆H₄CH=CH, (*E*)-MeCH=CH, Et, BnCH₂, *t*-Bu

proposed mechanism:



Scheme 7. Carboxycyanation of aldehydes with ethyl cyanoformate.

However, the most attractive cyanide source is inorganic cyanide salt KCN, which presents the advantage to be cheaper and avoids the involvement of toxic reagents. In this context, these authors reported in 2019 the first employment of KCN as the cyanide source in similar enantioselective carboxycyanations of aldehydes **13** catalyzed by the same bifunctional aluminum fluoride salen catalyst **24** [24]. This more practical carboxycyanation protocol was performed at -80 °C in the presence of 1.5 equivalent of KCN as the cyanation agent and 1 mol% of catalyst **24** in chloroform as the solvent. It provided cyanohydrins (*R*)-**26** with 85->99% yields and 55-95% ee, as presented in Scheme 8. The results were more or less comparable to those obtained with the original protocol using ethyl cyanoformate as the cyanide source (Scheme 7).

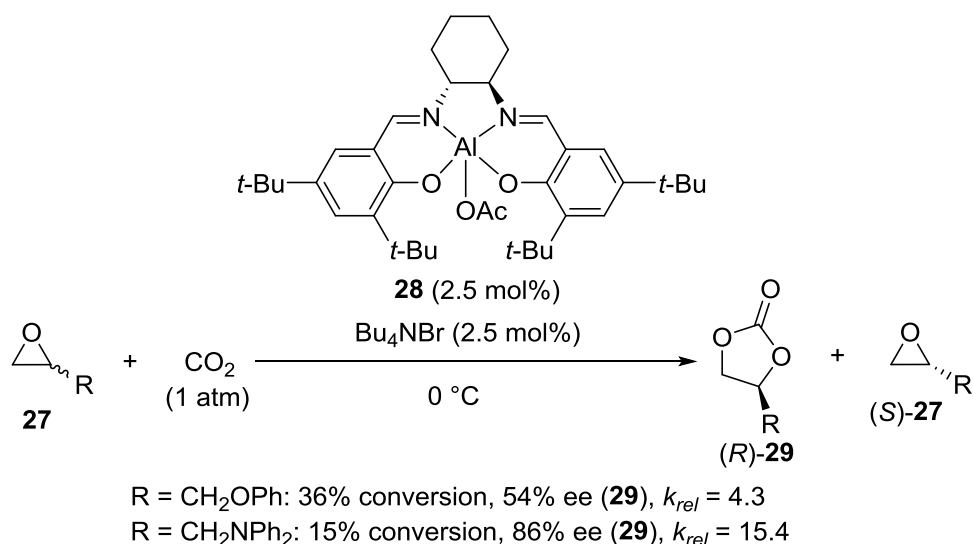


R = 2-Naph, 6-MeO-2-Naph, Ph, *p*-Tol, *m*-Tol, *o*-Tol, *p*-MeOC₆H₄,
m-MeOC₆H₄, *o*-MeOC₆H₄, 3,4-Me₂C₆H₃, 3,4-MeO₂C₆H₃, *p*-ClC₆H₄,
m-ClC₆H₄, *p*-FC₆H₄, *m*-MeO₂CC₆H₄, 2-furyl, 2-thienyl, (*E*)-PhCH=CH,
(*E*)-*p*-MeOC₆H₄CH=CH, (*E*)-MeCH=CH, Me, BnCH₂

Scheme 8. Carboxycyanation of aldehydes with KCN.

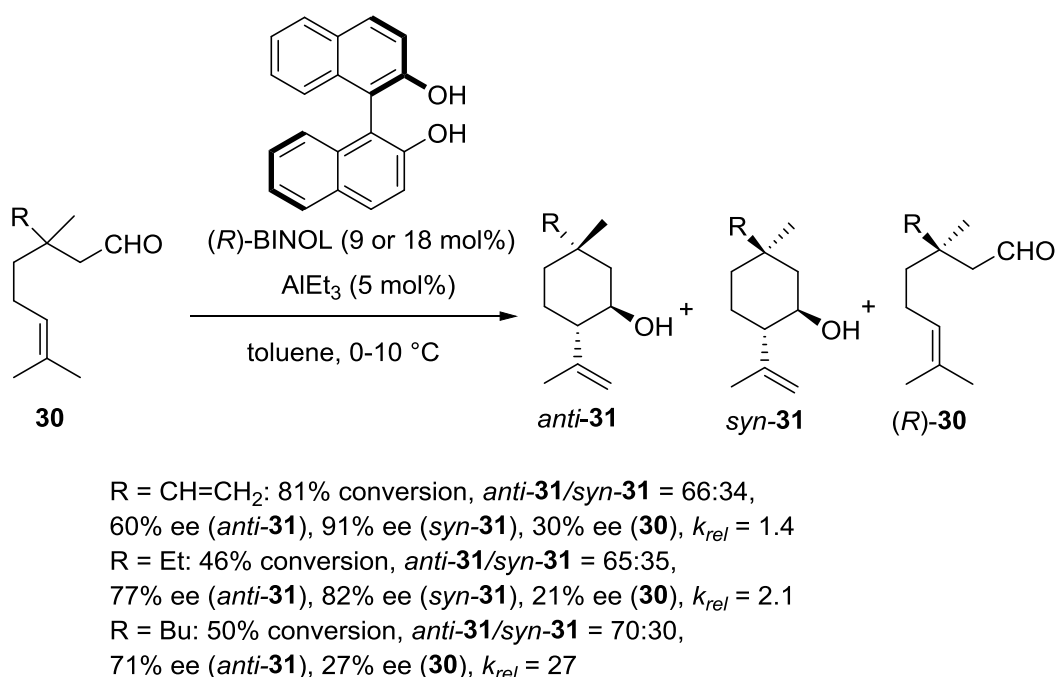
4. KINETIC RESOLUTIONS, DESYMMETRIZATIONS AND DERACEMIZATIONS

Among methodologies to access chiral compounds, simple kinetic resolution still constitutes the most efficient and practical approach especially in industry [25]. This methodology, often catalyzed by chiral salen cobalt or chromium complexes, has been extensively applied to achieve chiral epoxides, representing useful reagents in organic synthesis [26]. In 2015, North et al. reported the first aluminum-based catalyst capable of performing the kinetic resolution of epoxides through CO₂ coupling, affording chiral cyclic carbonates (Scheme 9) [27]. Indeed, the reaction of epoxides **27** performed under 1 atm of carbon dioxide pressure in the presence of 2.5 mol% of chiral aluminum complex **28** and the same quantity of Bu₄NBr as cocatalyst afforded in the absence of solvent the corresponding chiral cyclic carbonates (*R*)-**29** with moderate to good enantioselectivities (54-86% ee) and low conversions (15-36%) along with unreacted enantioenriched epoxides (*S*)-**27**. The *k_{rel}* values (4.3-15.4) were found higher than those obtained by using the analogous chromium and cobalt complexes arisen from the same ligand. The best *k_{rel}* value was achieved in the reaction of *N*-(2,3-epoxypropyl)diphenylamine as substrate (R = CH₂NPh₂).



Scheme 9. Kinetic resolution of epoxides through CO₂ coupling.

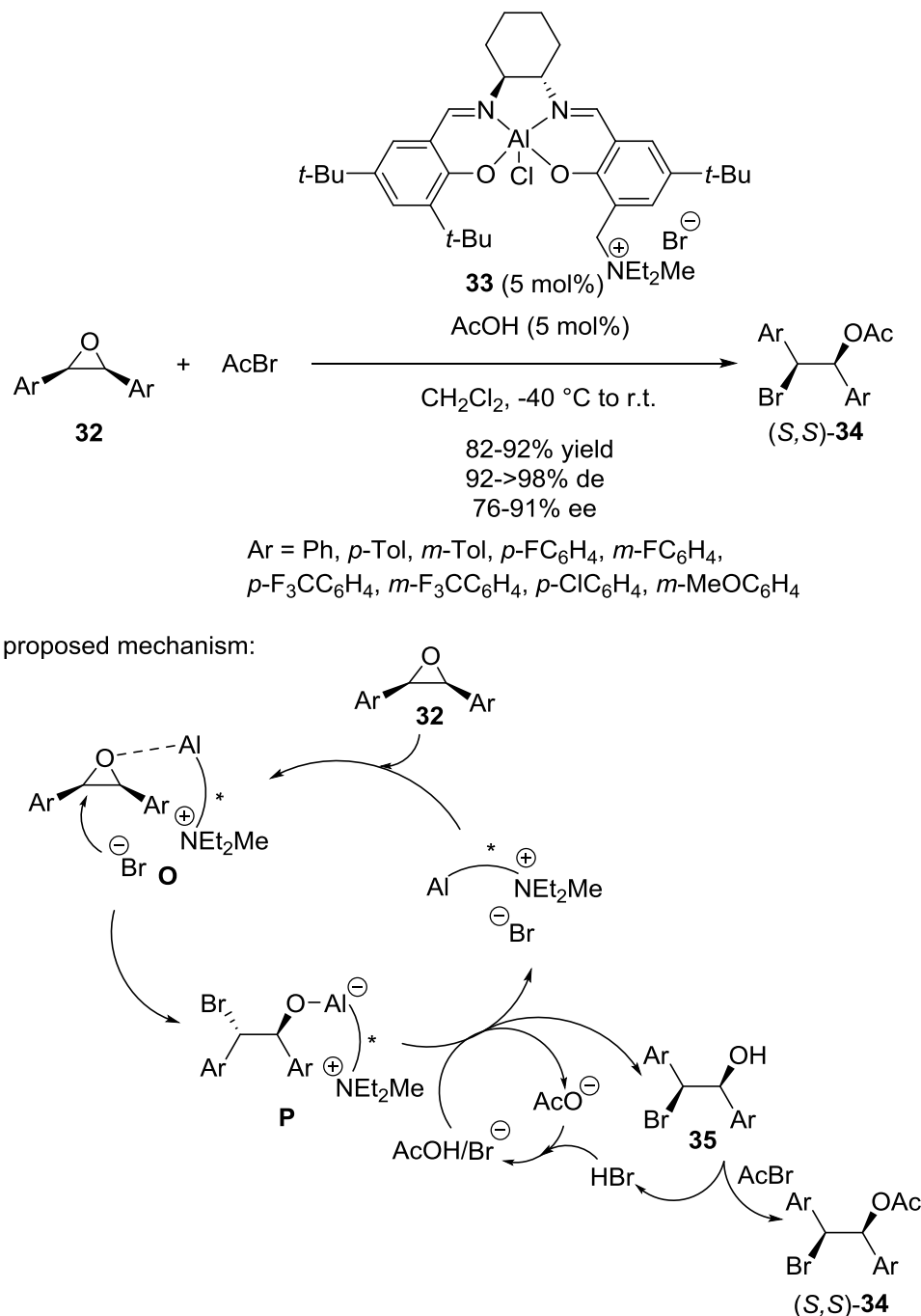
In 2016, Hori, Itoh and Mino described the kinetic resolution of citronellal analogues catalyzed by a chiral aluminum catalyst derived from 9 or 18 mol% of (*R*)-BINOL and 5 mol% of AlEt₃ [28]. The reaction evolved through cyclization of 3-alkylcitronellals **30**, leading to the corresponding chiral 5-alkylisopulegol derivatives **31** along with unreacted enantioenriched substrates (*R*)-**30** (Scheme 10). While the latter were obtained in low enantioselectivities (21-30% ee), cyclohexanols **31** were synthesized as mixtures of *anti*- and *syn*-diastereomers in 65:35 to 70:30 of *anti*/*syn* ratios with enantioselectivities of 82-91% ee for the *syn*-products and 60-77% ee for the *anti*-products. The best enantioselectivity (91% ee) was achieved in the reaction of 3-vinylcitronellal (R = CH=CH₂) to give chiral 5-vinylisopulegol.



Scheme 10. Kinetic resolution of citronellal analogues through cyclization.

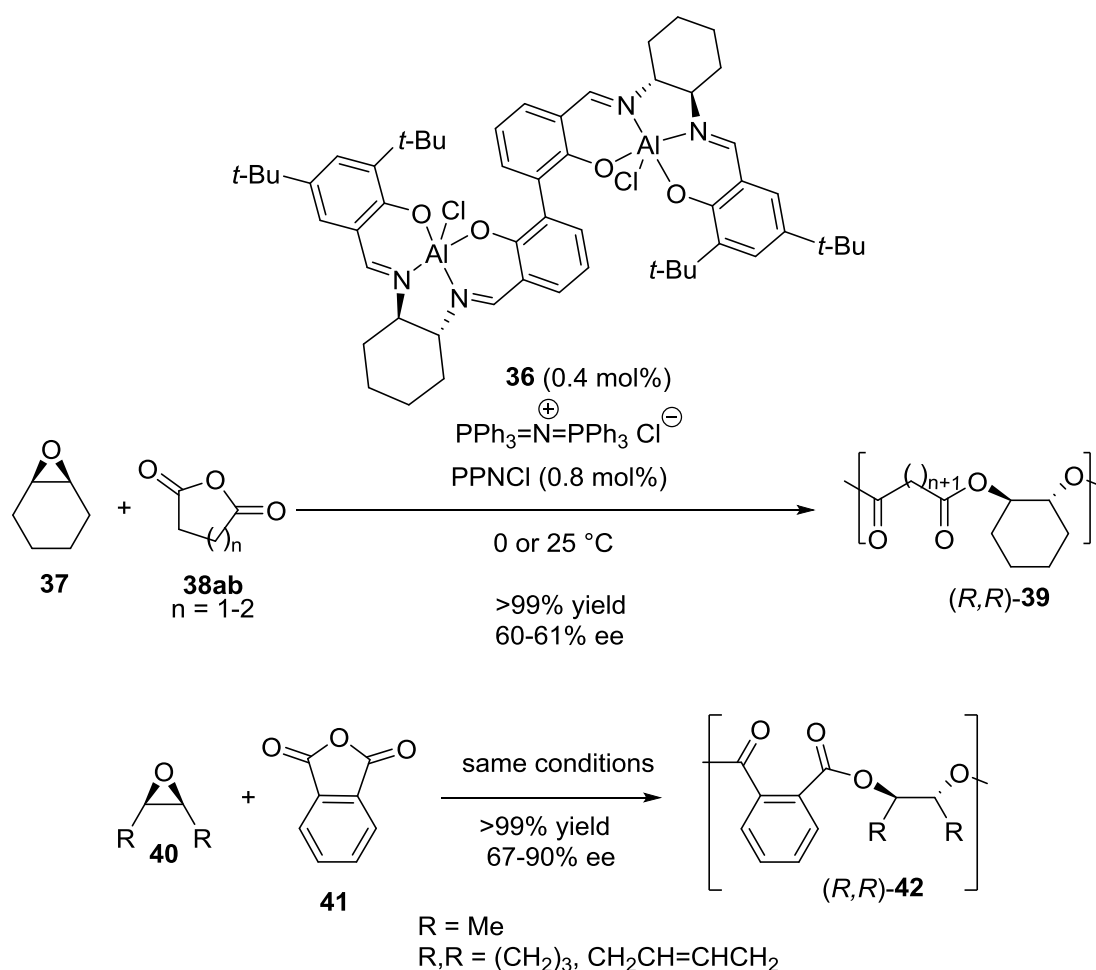
In spite of the high synthetic potential of chiral bromohydrins, the desymmetrization of *meso*-epoxides by bromide remains undeveloped. In 2017, Peters et al. described a novel methodology to prepare chiral *O*-acetyl protected bromohydrins based on enantioselective aluminum-catalyzed ring-opening of *meso*-epoxides **32** with AcBr [29]. The process occurred at -40 °C to room temperature in dichloromethane as solvent in the presence of 5 mol% of bifunctional aluminum chloride salen complex **33** exhibiting an appended ammonium salt and the

same quantity of AcOH as an additive. It resulted in the formation of chiral acetyl protected bromohydrins (*S,S*)-**34** in high yields (82-92%), diastereoselectivities (92->98% de) and enantioselectivities (76-91% ee), as illustrated in Scheme 11. The catalyst system was compatible with differently substituted aryl groups (Ar). Diastereomerically pure (>98% de) products were obtained from substrates bearing electron-withdrawing substituents while those with electron-donating ones provided lower diastereomeric ratios (Ar = *p*-Tol, *m*-Tol: 92% de). The highest enantioselectivities (90-91% ee) were achieved in the reaction of epoxides exhibiting a fluoro and *p*-CF₃ substituents on the phenyl ring. The lowest ee value (76% ee) was obtained in the reaction of an epoxide bearing a *m*-CF₃ substituent. The reaction evolved via the intermediate formation of bromohydrin **35** which was then acylated to give the final product, as shown in the mechanism depicted in Scheme 11. The latter shows the activation of the starting epoxide through coordination to the catalyst. The bromide anion occurred as nucleophile in intermediate **O**, thus forming aluminum intermediate **P**. Then, the latter underwent protonation in the presence of AcOH or HBr generated from the acylation step.



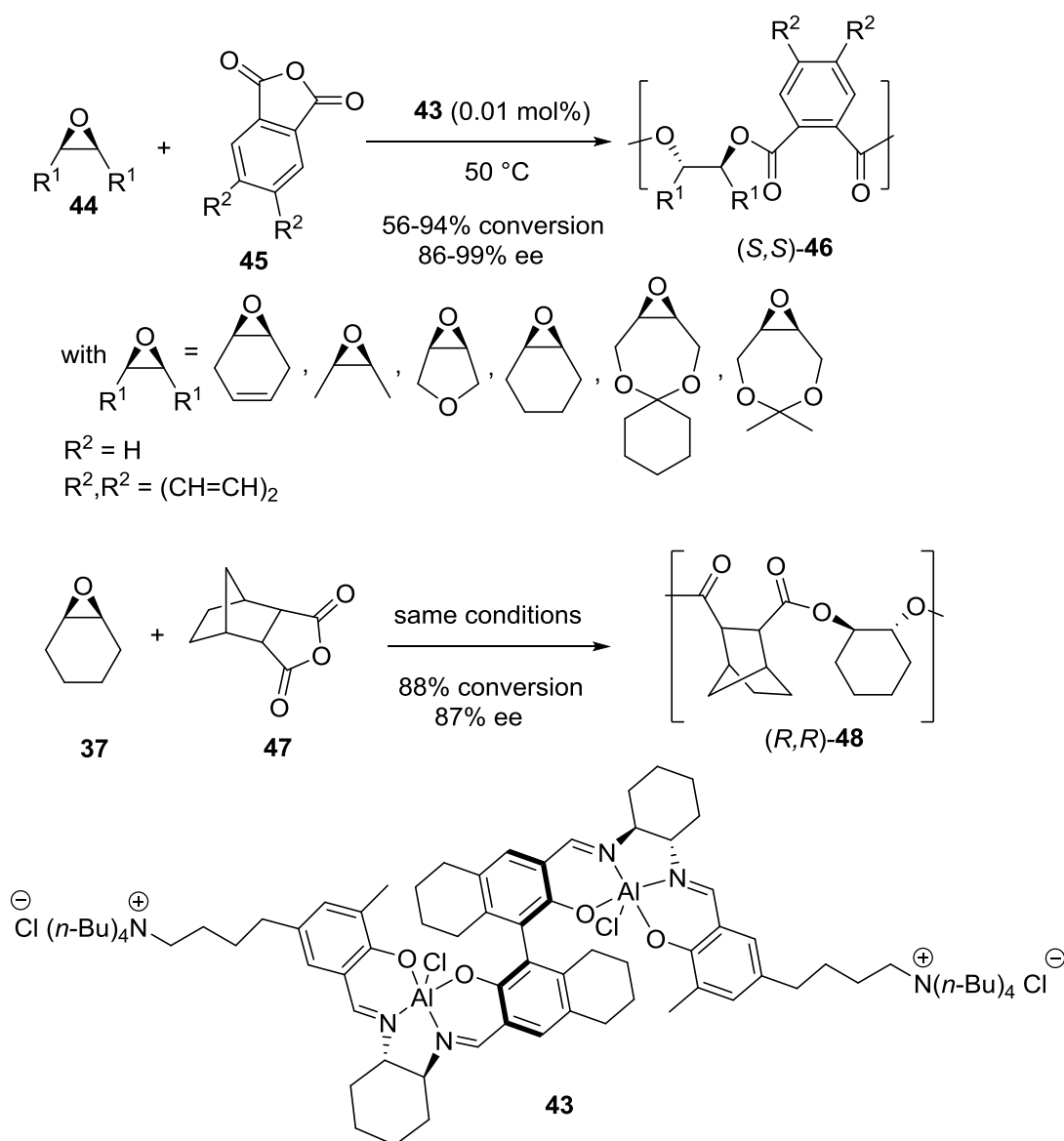
Scheme 11. Desymmetrization of *meso*-epoxides through ring-opening with AcBr.

Earlier in 2016, Lu et al. reported the first example of asymmetric copolymerization of *meso*-epoxides with cyclic anhydrides using chiral dinuclear aluminum salen complex **36**, which afforded stereoregular chiral polyesters with completely alternating structure and narrow molecular weight distribution [30]. As shown in Scheme 12, cyclohexene oxide **37** reacted with succinic anhydride **38a** ($n = 1$) or glutaric anhydride **38b** ($n = 2$) in the presence of only 0.4 mol% of chiral catalyst **36** and 0.8 mol% of bis(triphenylphosphine)iminium chloride (PPNCl) as cocatalyst to produce chiral polyesters (*R,R*)-**39** in quantitative yields and moderate enantioselectivities (60-61% ee). Better enantioselectivities (67-90% ee) combined with quantitative yields were achieved in the reaction of phthalic anhydride **41** with different epoxides **40**, such as cyclopentene oxide, *cis*-2,3-epoxybutane and 1,2-epoxy-4-cyclohexene, to give chiral polyesters (*R,R*)-**42**.



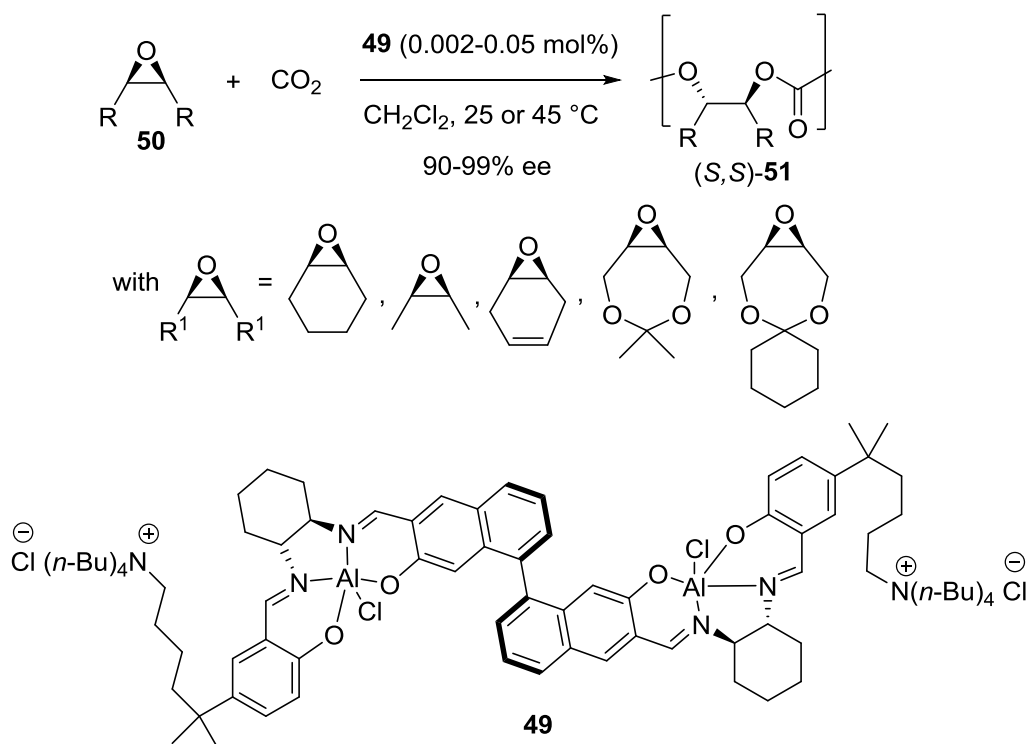
Scheme 12. Desymmetrizations of *meso*-epoxides through copolymerizations with cyclic anhydrides.

In 2022, these authors reinvestigated the same reactions by employing novel dinuclear chiral aluminum catalysts with multiple chiralities and ammonium salts anchored on the ligand [31]. These bifunctional catalysts, such as **43**, allowed uniformly excellent enantioselectivities (86-99% ee) to be achieved at a remarkably low catalyst loading (0.01 mol%). As shown in Scheme 13, the copolymerization of various *meso*-epoxides **44**, such as *cis*-2,3-epoxybutene, 1,2-epoxy-4-cyclohexene, 3,4-epoxytetrahydrofuran, 3,5,8-trioxaspiro[bicyclo-[5.1.0]-octane-4,1-cyclohexane], endo-4-phenyl-3,5,8-trioxabicyclo[5.1.0]octane (4-cy-dioxaeoxide), and 4,4-dimethyl-3,5,8-trioxabicyclo[5.1.0]octane, with cyclic anhydrides **45**, including phthalic anhydride and naphthyl anhydride, provided at 50 °C chiral polyesters (*S,S*)-**46** with perfectly alternating structure with moderate to excellent conversions (56-94%) and homogeneously excellent ee values (86-99% ee), as shown in Scheme 13. Moreover, the reaction of carbic anhydride **47** with 1,2-epoxy-4-cyclohexene **37** led to chiral polyester (*R,R*)-**48** with 88% yield and 87% ee.



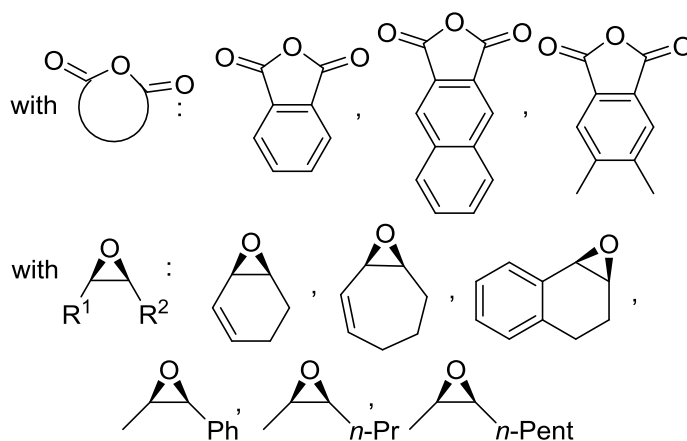
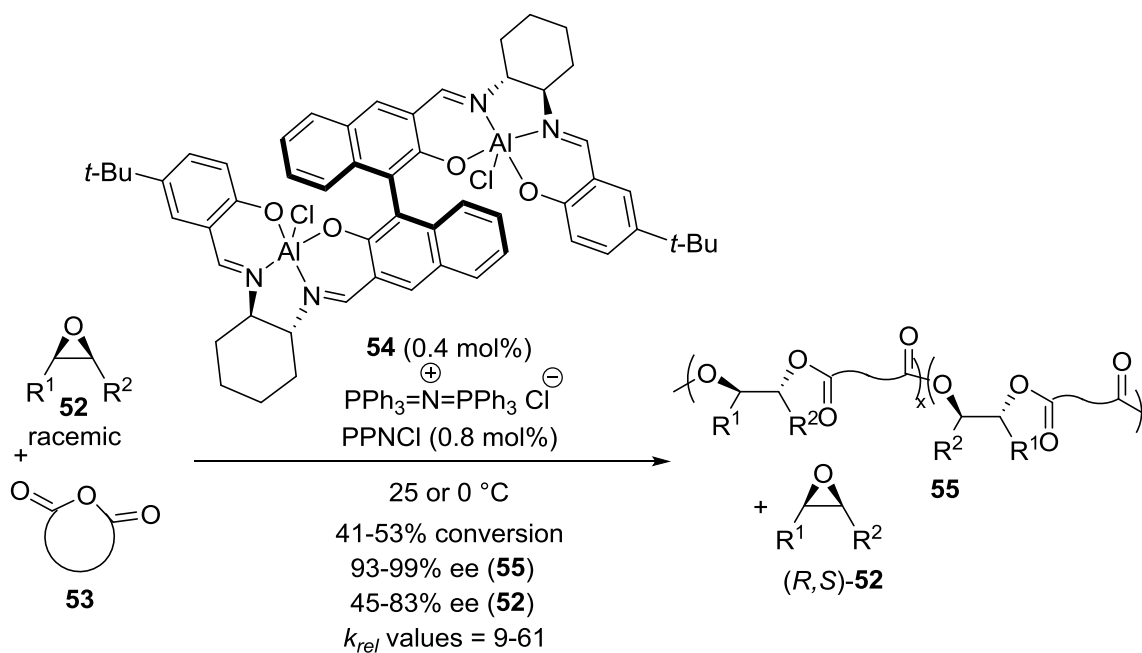
Scheme 13. Desymmetrizations of *meso*-epoxides through copolymerizations with cyclic anhydrides in the presence of a dinuclear aluminum catalyst tethered to quaternary ammonium salts.

In the same area, these authors designed related chiral binaphthol-linked bifunctional dinuclear aluminum catalysts featuring quaternary ammonium salts anchored on the ligand to be applied as promoters in asymmetric copolymerization of various *meso*-epoxides with CO_2 to synthesize the corresponding chiral isotactic polycarbonates (Scheme 14) [32]. When only 0.002-0.05 mol% of optimal chiral catalyst **49** was employed at 25 or 45 °C in dichloromethane as solvent to promote the copolymerization of a range of *meso*-epoxides **50** with CO_2 , it afforded the corresponding chiral polycarbonates $(S,S)\text{-51}$ with completely alternating structure and uniformly excellent enantioselectivities (90-99% ee).



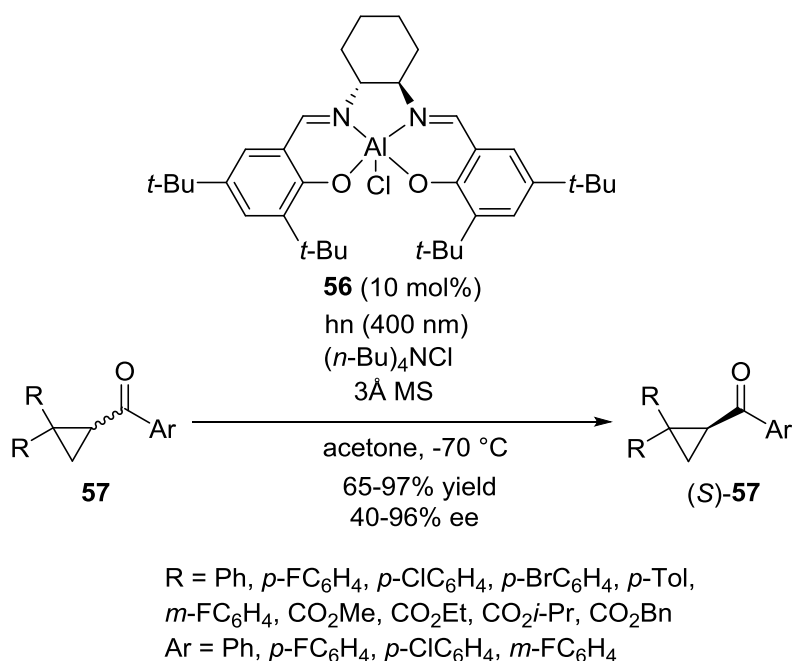
Scheme 14. Desymmetrization of *meso*-epoxides through copolymerization with CO₂ with a dinuclear aluminum catalyst tethered to quaternary ammonium salts.

In 2021, the same authors reported an unprecedented enantioselective copolymerization of racemic *cis*-internal epoxides **52** with cyclic anhydrides **53** mediated by chiral dinuclear aluminum catalyst **54** (0.4 mol%), affording the corresponding chiral polyesters **55**, along with unreacted epoxides (*R,S*)-**52** (Scheme 15) [33]. The reaction evolved at 25 or 0 °C through concomitant kinetic resolution of the epoxides with good conversions (41-53%) and k_{rel} values (9-61). The copolymers were obtained with uniformly excellent enantioselectivities (93-99% ee) while the recovered epoxides with moderate to good ee values (45-83% ee). Cyclic as well as acyclic epoxides were well tolerated.



Scheme 15. Kinetic resolution of racemic *cis*-internal epoxides with cyclic anhydrides through copolymerization.

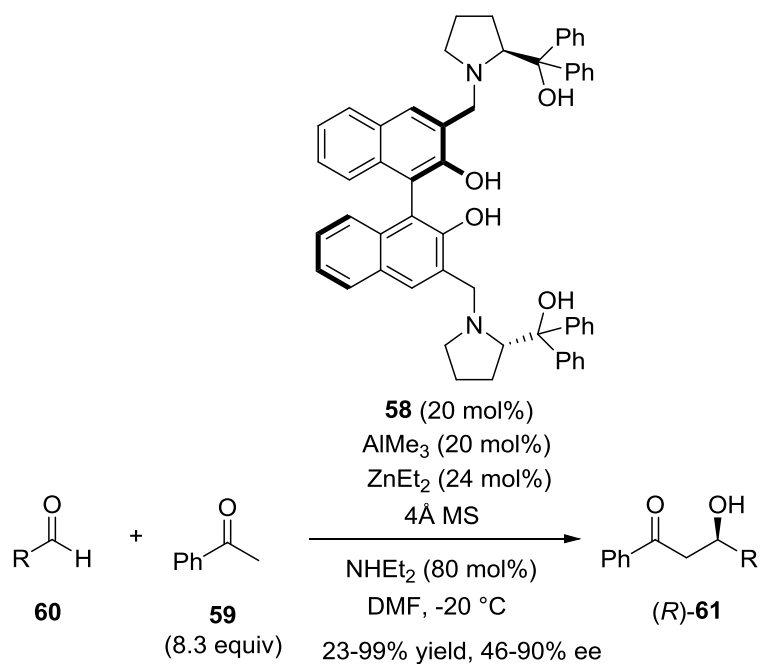
In 2023, Gilmour and Neugebauer reported the use of chiral aluminum salen complex **56** to perform a photochemical deracemization of cyclopropyl ketones with enantioselectivities of up to 96% ee (Scheme 16) [34]. Indeed, under irradiation at $\lambda = 400$ nm, a series of cyclopropyl ketones **57** could be deracemized at -70 °C in the presence of 10 mol% of catalyst **56** in acetone as solvent to afford enantioenriched ketones (*S*)-**57** with 65-97% yields and 40-96% ee. Both high yields (74-88%) and enantioselectivities (80-96% ee) were generally observed with *para*-substituted substrates (R) whereas a *meta*-substituted substrate (R = *m*-FC₆H₄) led to the corresponding product with 85% yield and 80% ee. In addition to *geminal* diaryl substituted cyclopropanes (R = aryl), several diester substrates (R = ester) were tolerated, leading to the corresponding products with 65-75% yields and 74-80% ee.



Scheme 16. Photochemical deracemization of cyclopropyl ketones.

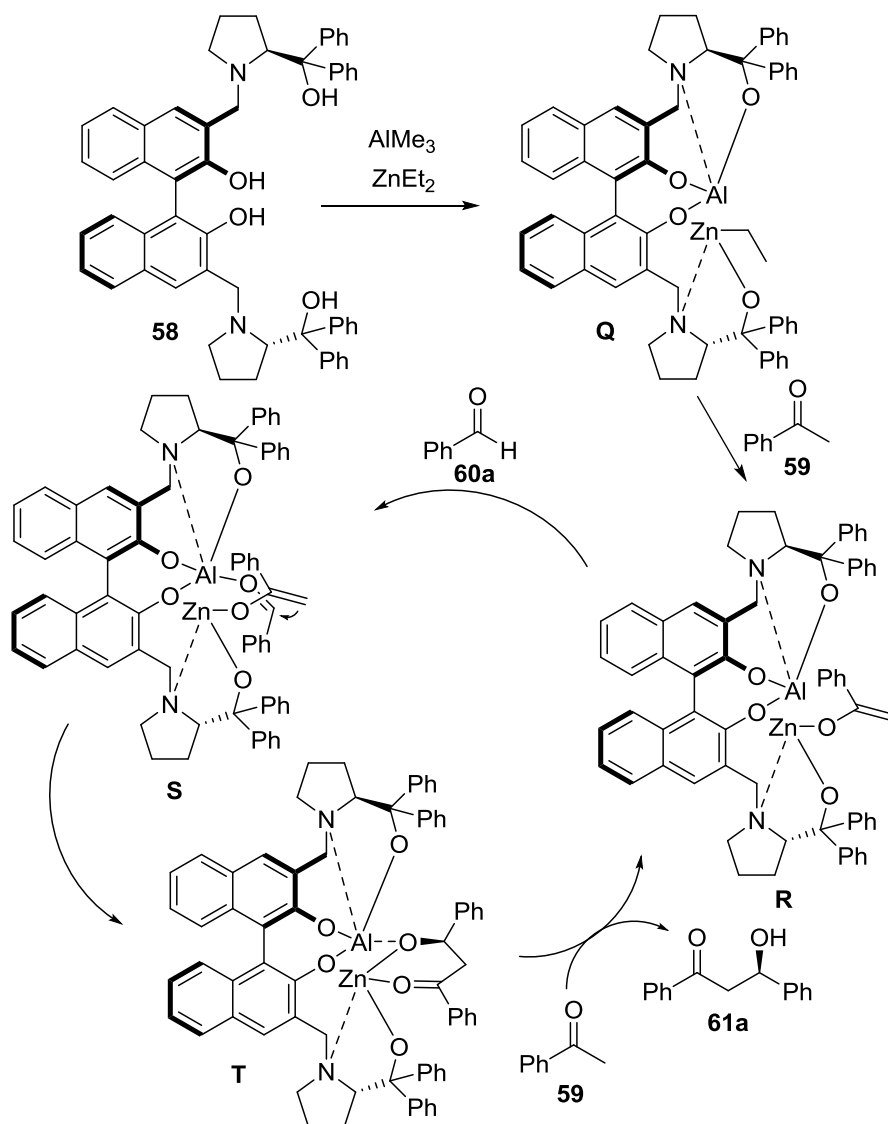
5. ALDOL REACTIONS

In 2016, Li et al. demonstrated that chiral bimetallic complexes based on aluminum and zinc could promote the direct enantioselective aldol condensation of aldehydes with acetophenone (Scheme 17) [35]. Among them, the optimal complex was in situ generated from 24 mol% of ZnEt₂, 20 mol% of AlMe₃, and 20 mol% of ligand **58** derived from (*R*)-BINOL. Performed at -20 °C in DMF as the solvent in the presence of NHEt₂ as an additive, the aldol reaction of acetophenone **59** with a range of aromatic as well as aliphatic aldehydes **60** led to the corresponding chiral β-hydroxy alcohols (*R*)-**61** in 23-99% yields and 46-90% ee. A range of aromatic aldehydes bearing either electron-donating or electron-withdrawing substituents on the phenyl ring were compatible, providing in most cases >80% ee values while lower ee values (46-56% ee) were observed in the reaction of aldehydes exhibiting *o*-chloro- and *o*-methoxy groups. On the other hand, the best enantioselectivity (90% ee) was obtained with 2-furaldehyde. Along with (hetero)aromatic aldehydes, aliphatic aldehydes also reacted smoothly, giving the desired chiral alcohols with moderate to good ee values (65-83% ee). The authors have proposed that the Al atom of the Al/Zn complex acted as a Lewis acid to activate aldehyde **60a**, while ethylzinc alkoxide interacted as a Brønsted base to form a reactive zinc enolate with acetophenone. This is shown in the mechanism proposed in Scheme 17, starting with the generation of heterobimetallic intermediate complex **Q** from semi-crown chiral ligand **58**, AlMe₃ and ZnEt₂. Then, acetophenone **59** reacted with complex **Q** to give reactive zinc enolate intermediate **R**. Further addition of benzaldehyde resulted in the formation of intermediate **S** in which the zinc enolate attacked benzaldehyde chelated to aluminum center from its *Re*-face to generate an *R*-configured chelated the aldol product in intermediate **T**. Then, the latter reacted with another molecule of acetophenone to give the final product **61a** along with regenerated intermediate **R**.



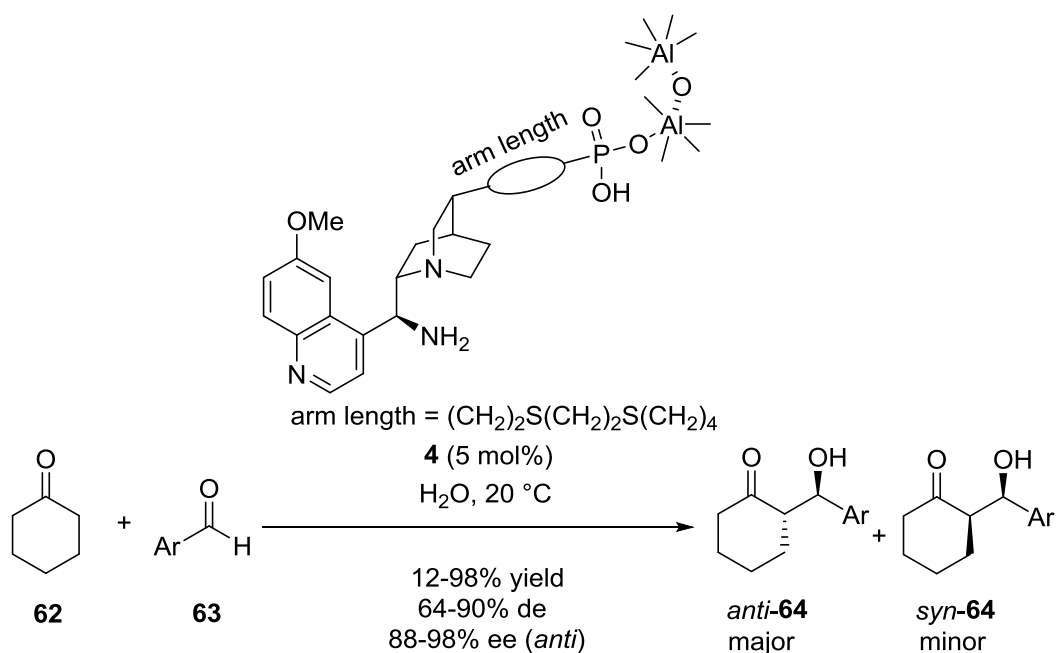
R = Ph, *p*-Tol, *m*-Tol, *o*-Tol, *p*-O₂NC₆H₄, *m*-O₂NC₆H₄,
o-O₂NC₆H₄, *p*-ClC₆H₄, *m*-ClC₆H₄, *o*-ClC₆H₄, *m*-MeOC₆H₄,
o-MeOC₆H₄, 1-Naph, 2-furyl, 2-thienyl, 3-thienyl, *i*-Pent, *n*-Bu

proposed mechanism (R = Ph):



Scheme 17. Aldol reaction of aldehydes with acetophenone.

In 2017, Ma et al. employed novel chiral cinchona alkaloid-tethered aluminum phosphonate complex **4** (Scheme 18) to promote green asymmetric aldol reaction of cyclohexanone **62** with benzaldehydes **63** performed in water at room temperature [14]. The reaction afforded the corresponding chiral β -hydroxy alcohols *anti*-**64** as major diastereomers with 64-90% de and 12-98% yields, as illustrated in Scheme 18. Uniformly excellent enantioselectivities (88-98% ee) were obtained for these major diastereomers. Various substituents were tolerated on the phenyl ring of benzaldehydes. While the presence of electron-withdrawing substituents resulted in the obtention of good to high yields (65-98%) and stereoselectivities (64-90% de and 92-98% ee), benzaldehydes bearing electron-donating groups provided lower yields (12-38%). Notably, this heterogeneous cooperative catalyst could be recovered and reused without significant loss of catalytic activity for up to ten runs.

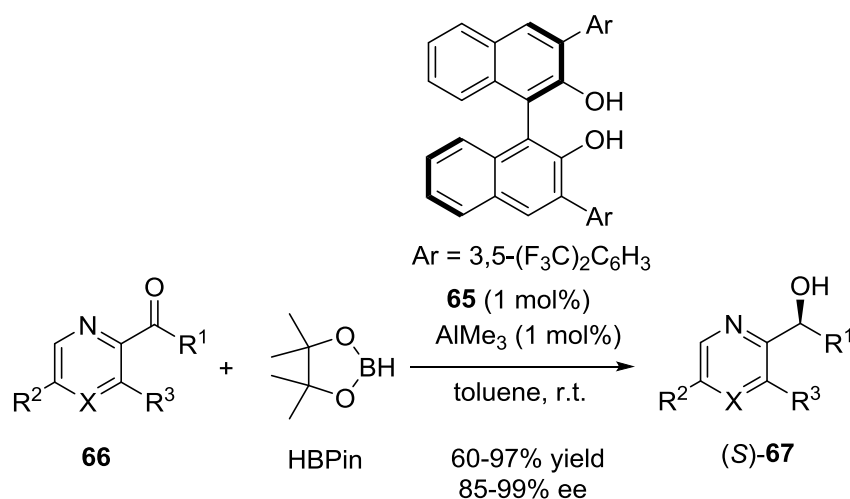


Ar = *o*-O₂NC₆H₄, *m*-O₂NC₆H₄, *p*-O₂NC₆H₄, *o*-NCC₆H₄, *p*-NCC₆H₄, *o*-ClC₆H₄,
m-ClC₆H₄, *p*-ClC₆H₄, *o*-Tol, *m*-Tol, *p*-Tol, *o*-MeOC₆H₄, *m*-MeOC₆H₄

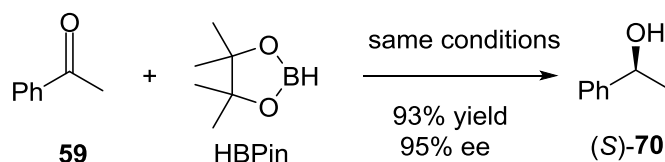
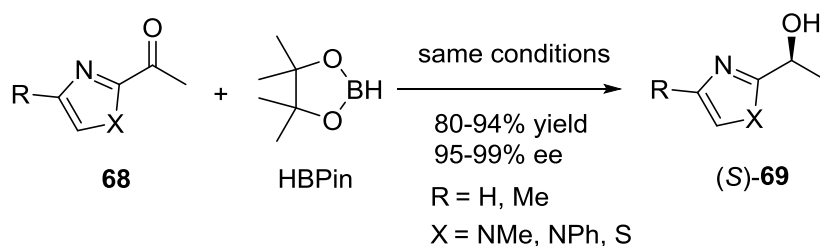
Scheme 18. Aqueous aldol reaction of cyclohexanone with benzaldehydes.

6. REDUCTIONS OF KETONES

Chiral 2-pyridine alcohols constitute important structural units in the pharmaceutical and agrochemical industries, as well as ligands in asymmetric metal catalysis. One simple protocol to prepare these molecules is based on the enantioselective reduction of the corresponding 2-pyridine ketones. In this context, Lebedev, Maity, Cavallo and Rueping reported in 2019 an asymmetric hydroboration of a wide range of 2-pyridine and analogous heterocyclic ketones, presenting the advantage to employ a very low catalyst loading of a chiral aluminum catalyst [36]. The latter was in situ generated from only 1 mol% of AlMe₃ and the same quantity of chiral BINOL-derived ligand **65** in toluene (Scheme 19). In this process performed at room temperature, HBPIn was selected as the borane, which reacted with a wide range of 2-pyridine ketones **66** (X = CH) to deliver chiral 2-pyridine alcohols (*S*)-**67** in 60-97% yields and 85-99% ee. The scope of the reaction could be extended to other heterocyclic ketones, such as pyrazine, imidazole, and thiazole derivatives **68**, leading to the corresponding chiral alcohols (*S*)-**69** with both high yields (80-94%) and enantioselectivities (95-99% ee). Moreover, the hydroboration of acetophenone **59** yielded the desired alcohol (*S*)-**70** in 93% yield and 95% ee. Importantly, the ligand could be recovered and reused.



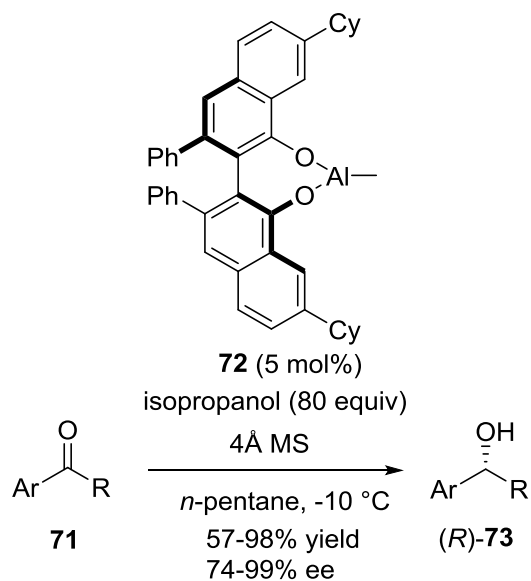
$\text{R}^1 = \text{Me}, n\text{-Oct}, i\text{-Bu}, \text{CH}_2=\text{CH}(\text{CH}_2)_2, \text{Ph}, p\text{-FC}_6\text{H}_4, 2\text{-thienyl},$
 $3\text{-thienyl}, 2\text{-furyl}, \text{N}^{\oplus}\text{S}^{\ominus}, \text{O}^{\ominus}(\text{CH}_2)_2$
 $\text{R}^2 = \text{H}, \text{Br}$
 $\text{R}^3 = \text{H}, \text{Et}$
 $\text{R}^1, \text{R}^3 = (\text{CH}_2)_2, (\text{CH}_2)_3$
 $\text{X} = \text{CH}, \text{CMe}, \text{N}$



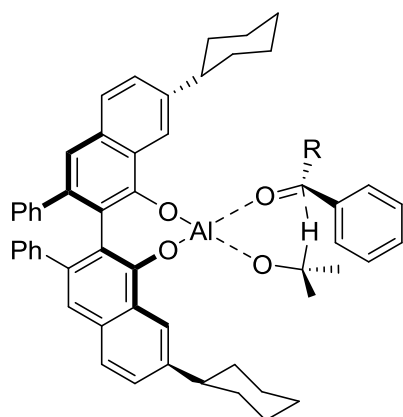
Scheme 19. Borohydride reductions of 2-pyridine ketones, five-membered heterocyclic ketones and acetophenone.

The use of inexpensive 2-propanol as a reducing agent as in the original Meerwein–Ponndorf–Verley reaction is very attractive in the reduction of ketones. In view of this, Wulff et al. developed in 2020 an enantioselective reduction of aryl alkyl ketones **71** using 2-propanol in the presence of 5 mol% of a chiral VANOL-derived aluminum catalyst **72** (Scheme 20) [37]. The latter was performed at room temperature in pentane from AlMe_3 and the corresponding chiral ligand. It allowed in pentane as solvent at $-10\text{ }^\circ\text{C}$ the formation of a range of chiral secondary alcohols (*R*)-**73** to be achieved in 57-98% yields and 74-99% ee. Many aromatic ketones exhibiting different substituents on the phenyl ring were compatible with most of them reduced with >90% ee values. Furthermore, excellent results were obtained in the reaction of various α -haloacetophenones, such as α -chloro-, α,α -dichloro-, α -bromo-, and α,α,α -trifluoroacetophenones. The lowest ee value (74% ee) was observed for propiophenone ($\text{R} = \text{Et}, \text{Ar} = \text{Ph}$). To explain the stereoselectivity of the process, the authors proposed the favored transition state depicted in Scheme 20 which did not present steric interaction between the cyclohexyl group on the catalyst and the phenyl group on the ketone ($\text{Ar} = \text{Ph}$) in comparison with the disfavored transition state. Even more interesting, the authors found that by using related chiral VANOL-derived aluminum catalyst **74**, it was possible to reduce, for the first time with an aluminum complex, simple dialkyl ketones **75**. Three aliphatic ketones led at -10 or $-20\text{ }^\circ\text{C}$ in the presence of 5 mol% of catalyst **74** and 2-propanol as the

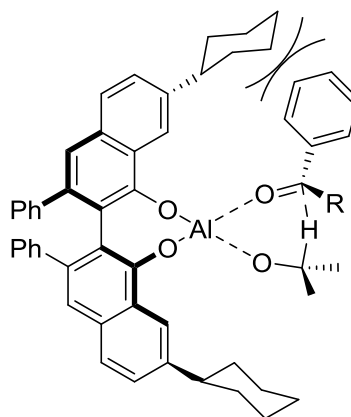
hydride donor in pentane to chiral secondary alcohols (*S*)-**76** in 81-87% yields and 82-94% ee. It was found that the highest enantioselectivity (94% ee) was reached in the reaction of the most sterically hindered ketone.



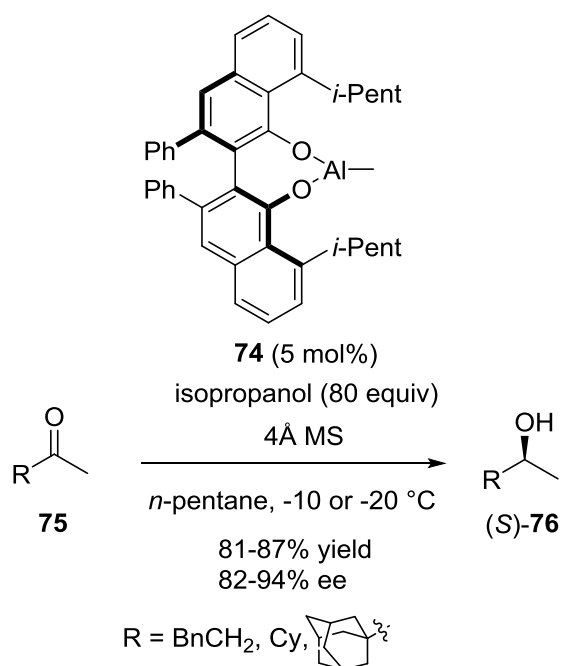
Ar = Ph, 2-Naph, 1-Naph, C₆F₅, *o*-ClC₆H₄, *o*-BrC₆H₄, *o*-IC₆H₄, *o*-Tol, *o*-MeOC₆H₄,
m-BrC₆H₄, *m*-Tol, *m*-MeOC₆H₄, *p*-NO₂NC₆H₄, *p*-F₃CC₆H₄, *p*-IC₆H₄, *p*-Tol, *p*-MeOC₆H₄
 R = Me, CF₃, ClCH₂, Cl₂CH, BrCH₂, Et



favored transition state (with Ar = Ph)

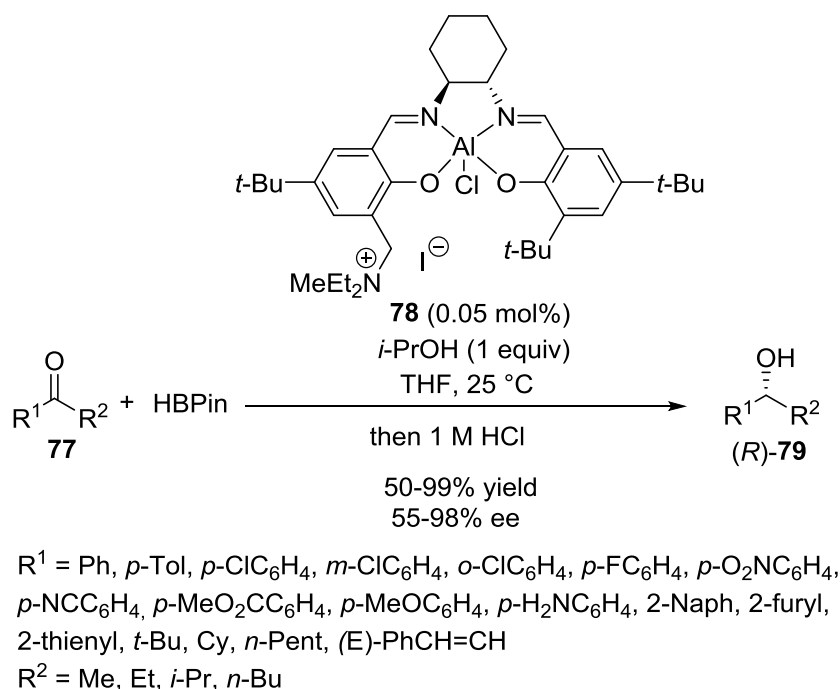


disfavored transition state (with Ar = Ph)



Scheme 20. Meerwein–Ponndorf–Verley reductions of ketones.

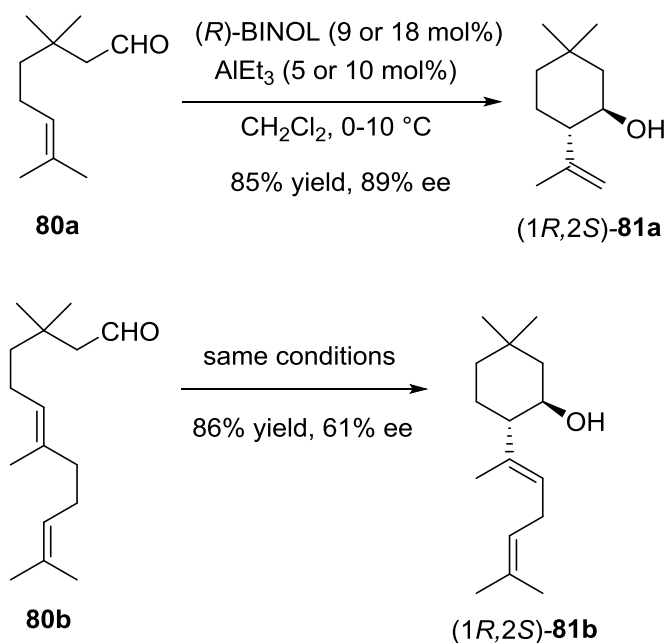
In 2021, Kästner and Peters achieved the enantioselective hydroboration of ketones **77** with pinacolborane in the presence of only 0.05 mol% of chiral salen catalyst **78** bearing an aprotic ammonium iodide (Scheme 21) [38]. The use of this highly active catalyst allowed a range of chiral secondary alcohols (*R*)-**79** to be synthesized with 50-99% yields and 55-98% ee in the presence of isopropanol as the proton source. The catalyst system tolerated (hetero)aryl alkyl as well as dialkyl ketones. Remarkably, high turnover numbers (TON = 15400) were achieved, being equivalent to an increase of activity of about 1.5 to >3 orders of magnitude compared to the most efficient asymmetric hydroboration catalysts. This was explained by the cooperative activation of the ketone by the Lewis acidic oxophilic metal center of the catalyst, and that of the borane reagent by the appended ammonium iodide moiety. This simultaneous activation of the two reactants explained the high catalytic activity of the aluminum complex.



Scheme 21. Borohydride reduction of (hetero)aryl alkyl and dialkyl ketones.

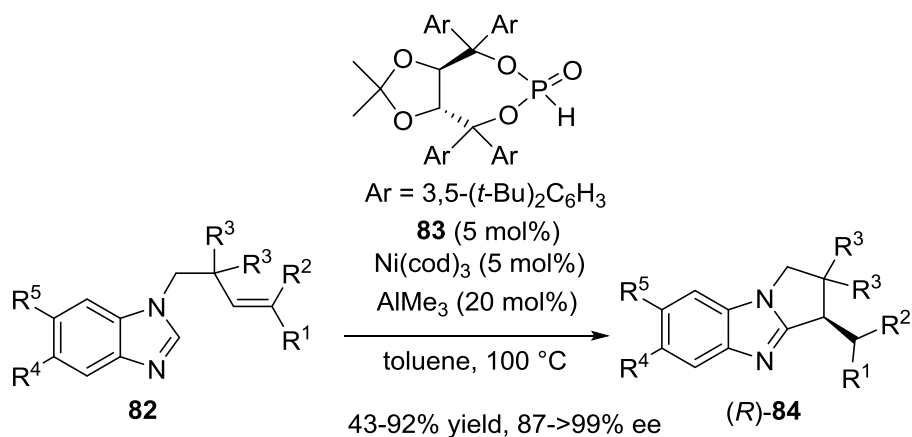
7. CYCLIZATIONS

In order to access chiral menthol derivatives, Hori and Mino applied in 2015 a chiral aluminum catalyst in situ generated from 5 or 10 mol% of AlEt_3 and 9 or 18 mol% of (*R*)-BINOL to promote asymmetric intramolecular ene reaction of unsaturated aldehydes **80ab** [39]. As shown in Scheme 22, the reaction carried out in dichloromethane at 0 to 10 °C gave access to chiral cyclohexanols (*1R,2S*)-**81ab** as single diastereomers (>99% de) with high yields (85-86%) and moderate to high enantioselectivities (61-89% ee). The best ee value (89% ee) was reached in the reaction of 3-methylcitronellal **80a**, giving chiral *trans*-5-methylisopulegol **81a**.



Scheme 22. Intramolecular ene reactions of unsaturated aldehydes.

In 2018, Ye et al. reported the first example of nickel/aluminum-catalyzed enantioselective *exo*-selective C–H cyclization of imidazole derivatives **82** with alkenes (Scheme 23) [40]. This process was induced by a chiral bimetallic Al/Ni catalyst in situ generated from 20 mol% of AlMe₃, 5 mol% of Ni(cod)₂, and 5 mol% of chiral phosphine oxide ligand **83**. Performed in toluene at 100 °C, it resulted in the formation of a wide range of bi- or polycyclic chiral imidazoles (*R*)-**84** exhibiting a β-stereocenter with generally good yields (43-92%) combined with homogeneously high enantioselectivities (87->99% ee). The substrate scope was remarkably wide, since it included *N*-containing heterocycles **85** (X = N, CO and Y = N, CO) which also delivered products (*R*)-**86** with 70-74% yields and 92-96% ee by using 15 mol% of additional ligand Ph₃P. Furthermore, simple imidazole-derived substrates **87** bearing an electron-withdrawing substituent (X = CO₂Me, Ac) underwent the reaction to give bicyclic imidazoles (*R*)-**88** with 85-90% yields and 88-93% ee. The authors proposed that the mechanism of the reaction involved the simultaneously chelation of the chiral ligand to the two metals (Ni and Al) and the substrate. As illustrated in Scheme 23, a ligand-to-ligand H transfer from the imidazole to the alkene occurred to generate (*R*)-**86**.



R¹ = Et, *i*-Pr, *n*-Pent, Me, H, Bn, Ph

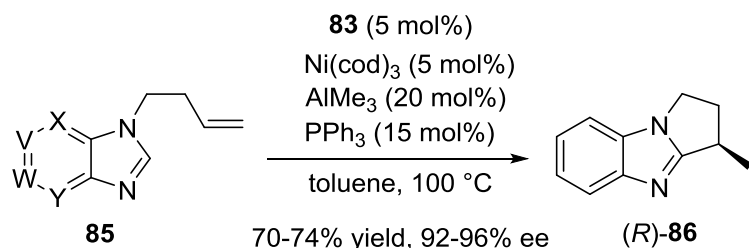
R² = H, Me, BnO(CH₂)₂

R³ = H, Me

R⁴ = H, Me, F, OMe, Cl, Br, CO₂Me, CF₃

R⁵ = H, Me, OLe, Cl

R⁴, R⁵ = (CH=CH)₂

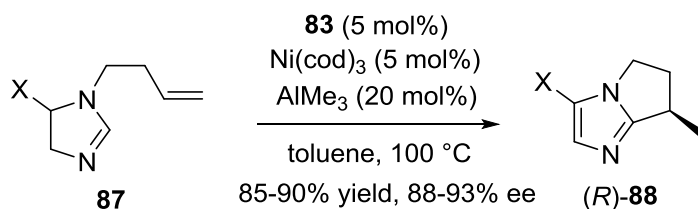


X = CH, N, CO

Y = CH, N, CO

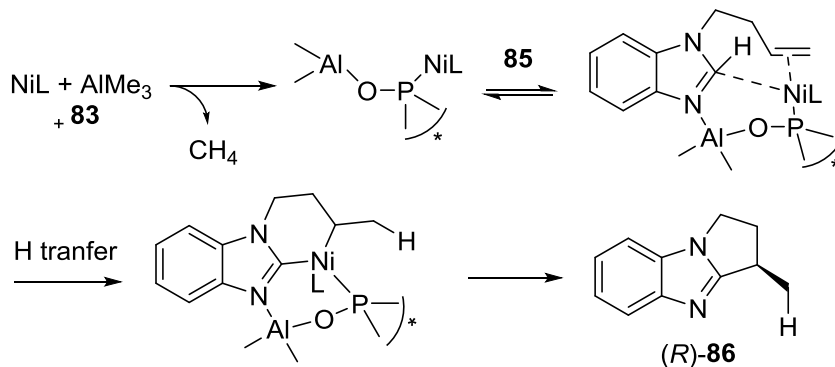
V = CH, NMe

W = CH, NMe



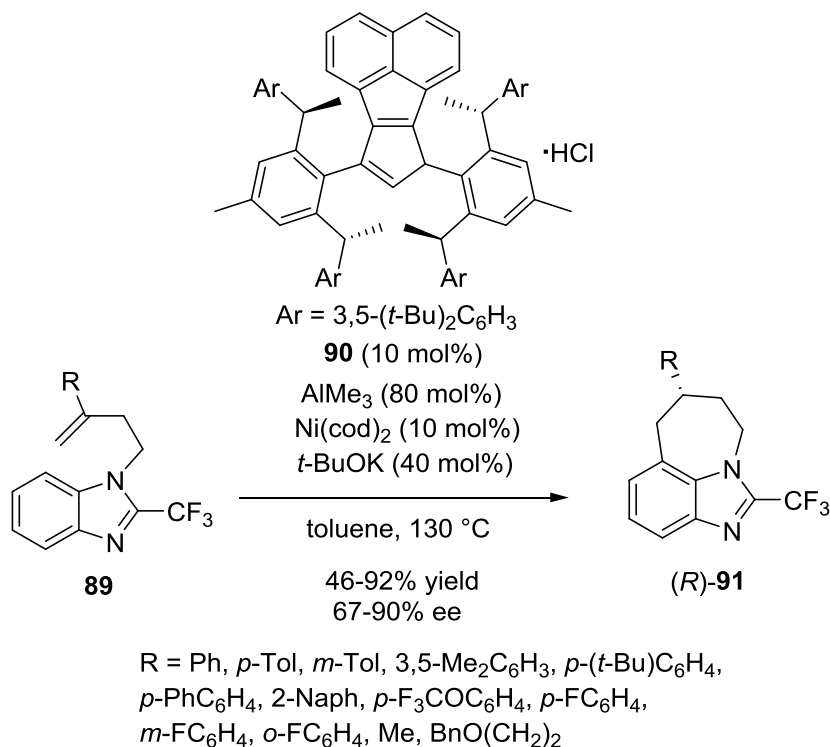
X = CO₂Me, Ac

mechanism for the formation of **(R)-86**:



Scheme 23. *Exo*-selective C–H cyclizations of imidazole derivatives with alkenes.

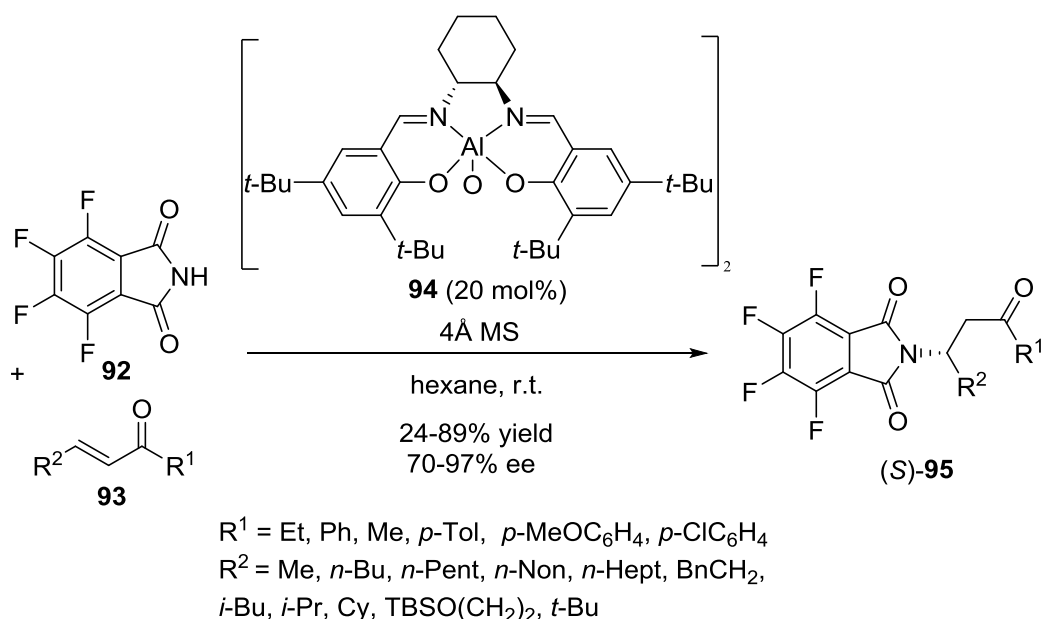
With the aim of developing a novel route to chiral tricyclic imidazoles bearing a seven-membered ring which constitute the structural motifs of many bioactive molecules, the same authors reported in 2021 a direct construction of seven-membered rings through enantioselective unreactive C7–H cyclization of benzoimidazoles **89** with alkenes [41]. As shown in Scheme 24, these substrates exhibiting a trifluoromethyl group at the C2 position underwent an *endo*-selective C7–H bond cyclization in the presence of a combination of 10 mol% of Ni(cod)₂, 80 mol% of AlMe₃ and 10 mol% of bulky chiral ligand **90**·HCl as catalyst system. The reaction was performed in toluene at 130 °C with 40 mol% of *t*-BuOK, thus producing a variety of chiral tricyclic imidazoles (*R*)-**91** with 46-92% yields and 67-90% ee.



Scheme 24. *Endo*-selective C7–H bond cyclization of benzoimidazoles with alkenes.

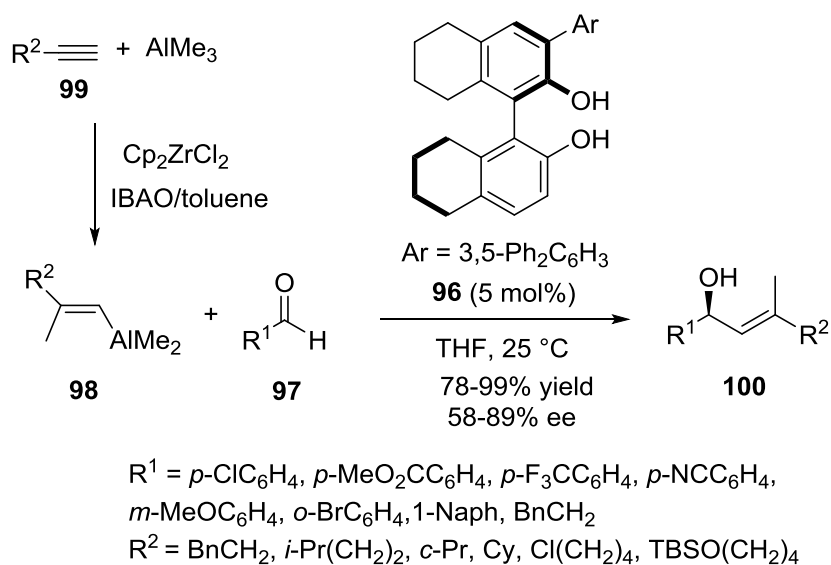
8. MISCELLANEOUS REACTIONS

The first example of enantioselective aluminum-catalyzed Michael-type reaction was described in 1999 by Jacobsen and Myers, dealing with the conjugate addition of hydrazoic acid to α,β -unsaturated imides which was achieved with up to 97% ee [42]. More recently in 2015, Szpilman et al. reported a highly enantioselective aza-Michael addition of tetrafluorophthalimide **92** to α,β -unsaturated ketones **93** catalyzed by chiral dinuclear salen aluminum complex **94** (Scheme 25) [43]. The transformation was carried out at room temperature in hexane with the involvement of 20 mol% of this salen μ -oxo aluminum complex, which afforded chiral amino ketones (*S*)-**95** in 24-89% yields and 70-97% ee. This work constituted the first example of a conjugate addition of tetrafluorophthalimide as a masked amine. The catalyst system was compatible with both alkyl and aryl groups in the R¹ position of α,β -unsaturated ketone **93**, as well as alkyl groups in the R² position. Notably, even sterically hindered substituents, such as isopropyl (70% yield, 89% ee) or cyclohexyl (24% yield, 97% ee), were tolerated in the R² position, despite their proximity to the unsaturated acceptor carbon. Furthermore, *tert*-butyl-substituted enones (R² = *t*-Bu) reacted to form the corresponding products with 55-61% yields and 86-90% ee, albeit requiring long reaction times (up to 3 days). The tetrafluorophthalimide group could be easily removed under mild chemoselective conditions by treatment with hydrazine in methanol to afford in quantitative yields the corresponding free primary β -amino ketones which are of great utility in the synthesis of important products.



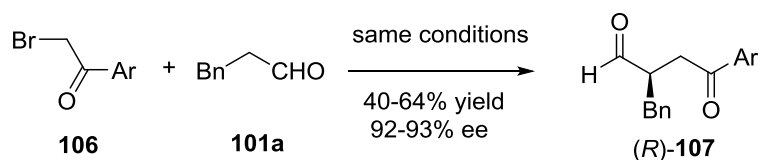
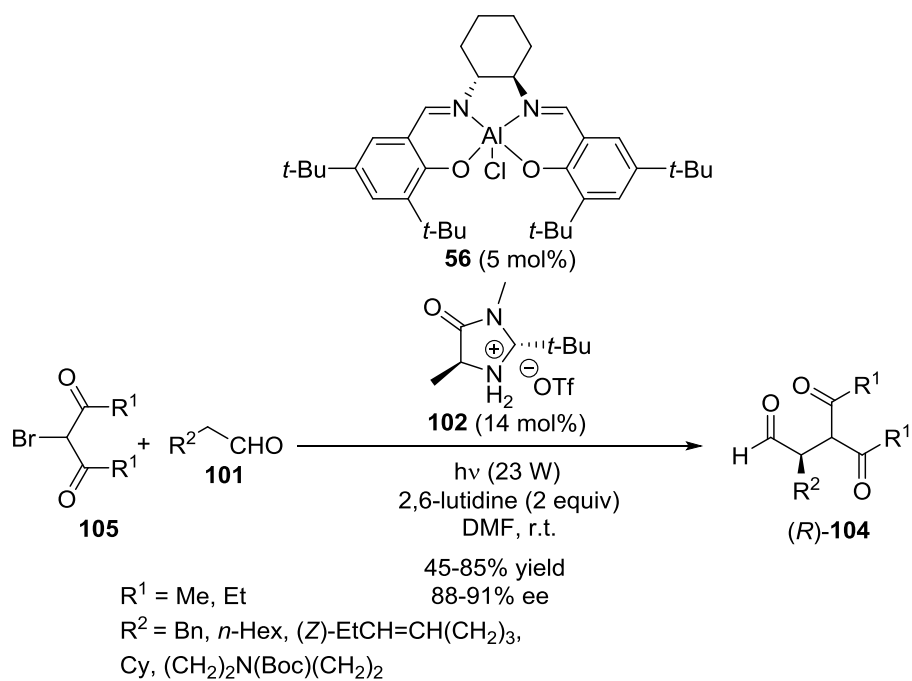
Scheme 25. Aza-Michael addition of tetrafluorophthalimide to α,β -unsaturated ketones.

In 2016, a chiral aluminum catalyst system derived from chiral H_8 -BINOL-derived ligand **96** was employed by Harada et al. to promote the enantioselective vinylation of aldehydes **97** [44]. The required β,β -disubstituted vinylaluminum reagents **98** were in situ generated through zirconium-catalyzed carboalumination of the corresponding terminal alkynes **99** with Me_3Al in the presence of isobutylaluminumoxane (IBAO), as presented in Scheme 26. The vinylaluminum reagent further underwent, at 25 °C in the presence of 5 mol% of chiral ligand **96** in THF as solvent, enantioselective addition to a variety of aldehydes **97** to give the corresponding generally (*S*)-configured allylic alcohols **100** in 78-99% yields and 58-89% ee. A range of aromatic aldehydes were compatible with the highest ee values (74-89% ee) obtained in the reaction of *para*- and *meta*-substituted benzaldehydes while *ortho*-substituted ones provided lowest enantioselectivities ($R^1 = o\text{-BrC}_6\text{H}_4$: 58% ee) as well as 1-naphthaldehyde ($R^1 = 1\text{-naphthyl}$: 58% ee). Interestingly, the catalyst system was also effective with an aliphatic aldehyde ($R^1 = \text{BnCH}_2$) which produced in this case of substitution the (*R*)-product with 69% ee. Concerning the alkyne partner, in addition to 4-phenylbut-1-yne ($R^2 = \text{Bn(CH}_2)_2$), branched and cycloalkyl-substituted terminal alkynes ($R^2 = i\text{-Pr(CH}_2)_2$, cyclohexyl, cyclopropyl) delivered the corresponding chiral allylic alcohols with 74-81% ee. The authors showed that shifting aluminum to titanium catalyst derived from the same ligand, resulted in the formation of the desired enantiomeric allylic alcohols.

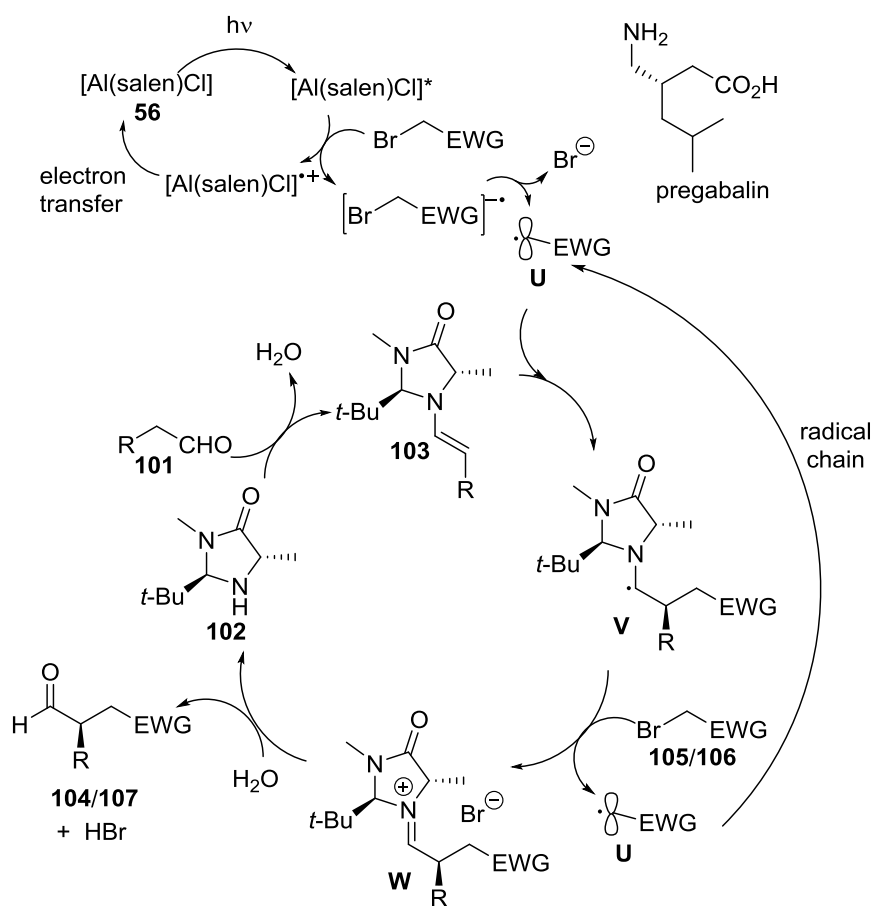


Scheme 26. Addition of vinylaluminum reagents to aldehydes.

In 2020, Gualandi, Ceroni and Cozzi demonstrated that chiral aluminum salen complex **56** could be employed as photoredox catalyst in the enantioselective reaction of aliphatic aldehydes **101** with α -bromo carbonyl compounds, thus forming α -alkylated chiral products (Scheme 27) [45]. The reaction was performed at room temperature in DMF in the presence of 14 mol% of chiral imidazolidine salt **102**, 5 mol% of aluminum catalyst **56** and 2,6-lutidine as base under visible light irradiation. Chiral imidazoline **102** was used as organocatalyst which formed chiral enamine **103** by reaction with aldehyde **101** while the chiral aluminum complex in its excited state directly reduced the bromine derivative, thus leading to radical species **U** after debromination. As depicted in the catalytic cycle proposed in Scheme 27, radical **U** subsequently reacted with chiral enamine **103** to give intermediate **V**. The latter reaction was the enantiodiscriminating step of the process. Then, intermediate **V** generated iminium intermediate **W** which delivered the final product and regenerated organocatalyst. Merging organocatalysis with this aluminum-catalyzed photoredox process allowed a series of chiral α -alkylated aldehydes (*R*)-**104** to be synthesized in 45-85% yields and 88-91% ee from the corresponding aliphatic aldehydes **101** and dimethyl/diethylbromomalonates **105**. The extension of this methodology to α -bromo ketones **106** produced, by reaction with 3-phenylpropanal **101a**, chiral α -benzylated aldehydes (*R*)-**107** with moderate yields (40-64%) albeit associated to high ee values (92-93% ee). The authors demonstrated the radical nature of the reaction by the fact that it was inhibited in the presence of oxygen or TEMPO. This novel procedure was applied to the development of a formal synthesis of antiepileptic drug pregabalin.

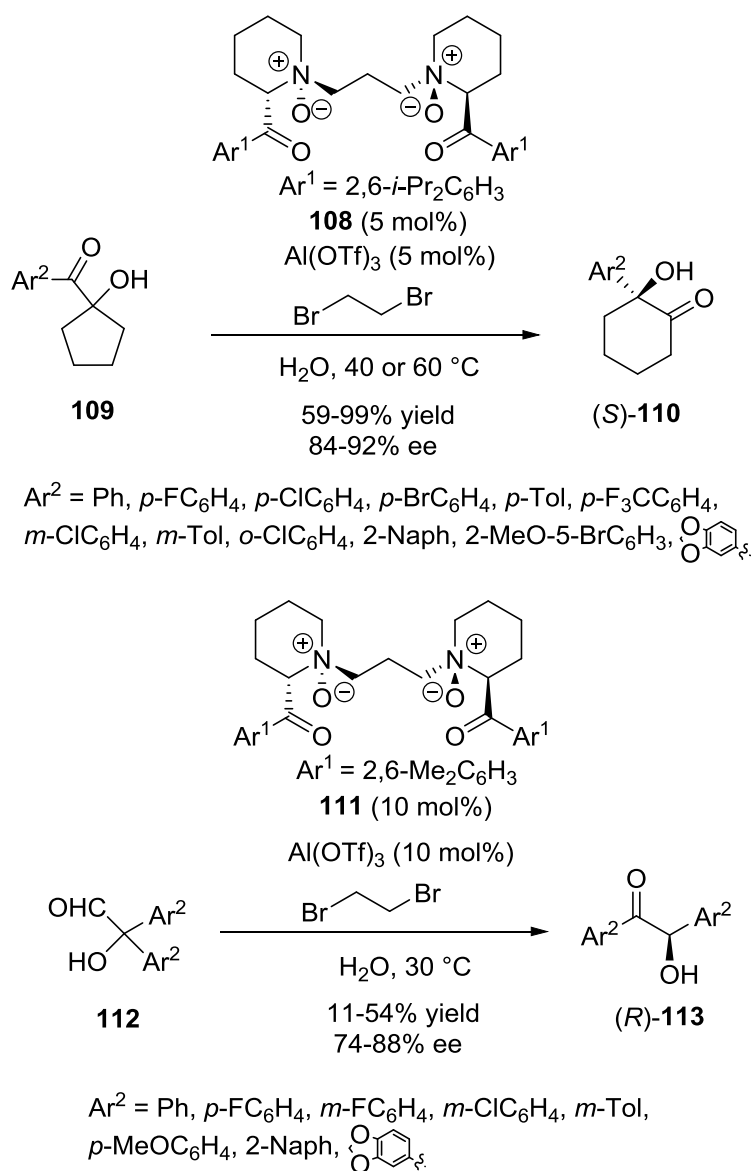


proposed mechanism for reaction of RCH_2CHO with BrCH_2EWG :



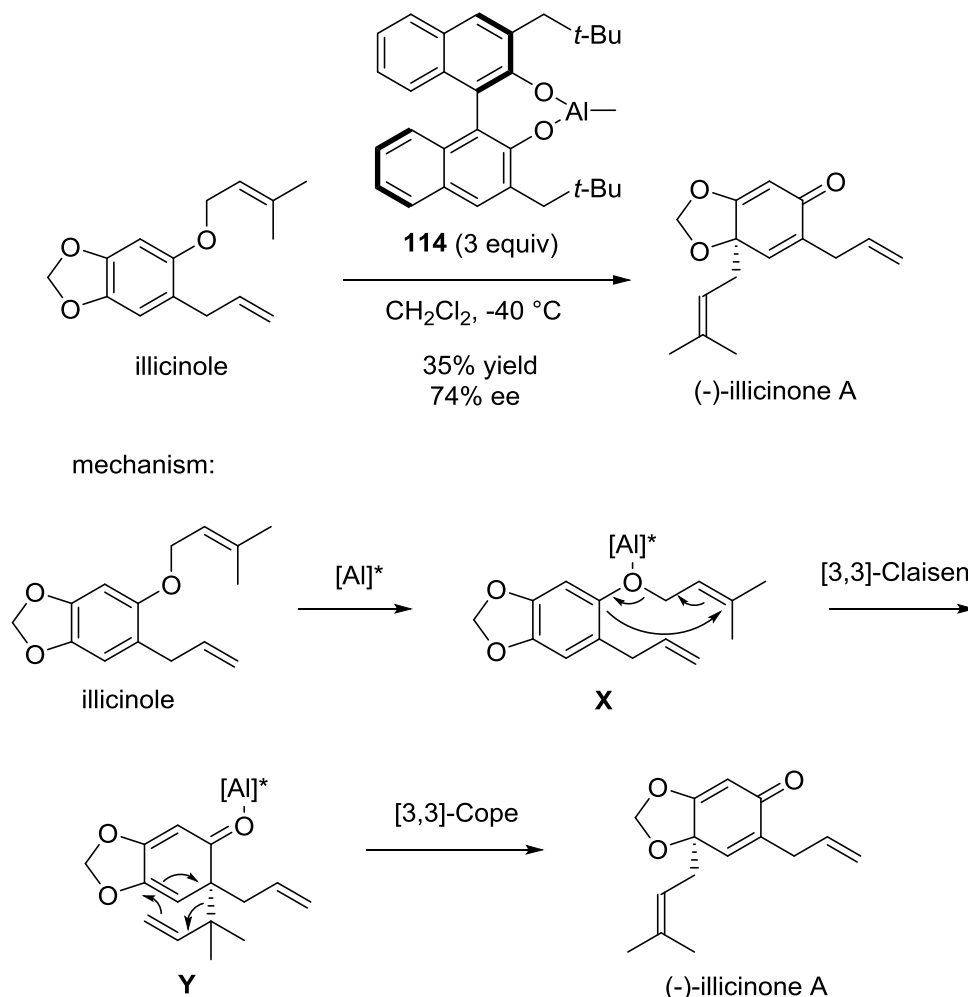
Scheme 27. α -Alkylations of aliphatic aldehydes with dialkylbromomalonates/ α -bromo ketones.

In another area, Zhou and Feng demonstrated in 2020 that a chiral aluminum catalyst derived from 5 mol% of *N,N'*-dioxide chiral ligand **108** and the same quantity of $\text{Al}(\text{OTf})_3$ as precatalyst was capable of promoting enantioselective acyloin rearrangements of cyclic α -ketols **109** [46]. The process was performed at 40 or 60 °C in 1,2-dibromoethane as the solvent, resulting in the formation of chiral α -hydroxy cyclohexanones (*S*)-**110** in 59-99% yields and 84-92% ee, as illustrated in Scheme 28. The electronic nature of the substituents exhibited on the phenyl group (Ar^2) had no influence on the enantioselectivity of the reaction while the presence of a strong electron-withdrawing group at the *para*-position ($\text{Ar}^2 = p\text{-CF}_3\text{C}_6\text{H}_4$) or a methyl substituent at the *meta*-position ($\text{Ar}^2 = m\text{-Tol}$) in the substrate led to lower yields (59-67%). In the reaction of a disubstituted aryl ring ($\text{Ar}^2 = 2\text{-MeO-5-BrC}_6\text{H}_3$), the reaction required a higher temperature (60 °C instead of 40 °C) to afford the corresponding product with 97% yield and 91% ee. In the presence of another chiral aluminum catalyst in situ generated from 10 mol% of closely related chiral *N,N'*-dioxide ligand **111** and the same quantity of $\text{Al}(\text{OTf})_3$, a series of α -hydroxy aldehydes **112** also underwent enantioselective acyloin rearrangement at 30 °C to afford the desired chiral acyclic α -hydroxy ketones (*R*)-**113** in low to moderate yields (11-54%) and good to high ee values (74-88% ee). Generally, aryl-substituted alcohols with substituents at the *para*-position yielded the expected products in higher yields than those with *meta*-substituted ones (39-49% vs 11-26%).



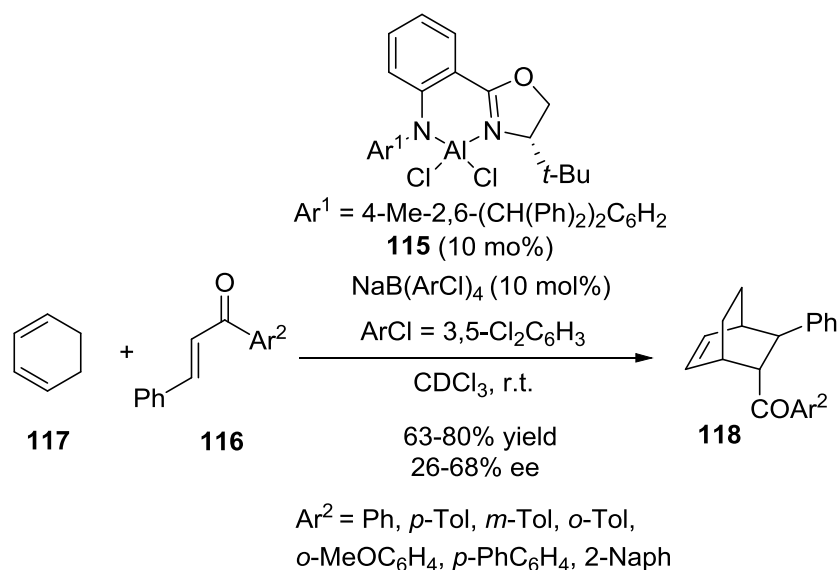
Scheme 28. Acyloin rearrangements of cyclic α -ketols and α -hydroxy aldehydes.

The first total synthesis of natural product (-)-illicinone A was disclosed in 2021 by Lawrence et al. by using a superstoichiometric quantity (3 equiv) of BINOL-derived chiral aluminum complex **114** [47]. The process involved the asymmetric *para*-Claisen rearrangement of illicinole performed at -40 °C in dichloromethane as solvent, resulting in the formation of (-)-illicinone A in moderate yield (35%) and 74% ee (Scheme 29). A possible mechanism detailed in Scheme 29 evolved through chelation of illicinole with the aluminum catalyst to give intermediate **X** which was then submitted to [3,3]-Claisen rearrangement to afford intermediate **Y**. The latter species subsequently underwent [3,3]-Cope rearrangement to provide desired (-)-illicinone A.



Scheme 29. *Para*-Claisen rearrangement of illicinole.

In 2023, Vidovic et al. reported the synthesis of novel preformed chiral oxazoline-containing aluminum dichloro complexes to be investigated as promoters in enantioselective Diels–Alder reactions of 1,3-cyclohexadiene with chalcones [48]. Among a series of catalysts, complex **115** exhibiting a *tert*-butyl group connected to the stereogenic center of the oxazoline fragment was selected as optimal. As shown in Scheme 30, promoted by 10 mol% of chiral catalyst **115** in the presence of the same quantity of NaBArCl₄ (ArCl = 3,5-Cl₂C₆H₃), a series of chalcones **116** reacted at room temperature in CDCl₃ as solvent with cyclohexadiene **117** to afford the corresponding chiral cycloadducts **118** as single *endo*-diastereomers (>98% de) with good yields (63–80%) and moderate enantioselectivities (26–68% ee). The best ee value (68% ee) was achieved in the reaction of chalcone (Ar² = Ph) while substituted chalcones resulted not only in lower enantioselectivities (26–53% ee) but also in longer reaction times. It must be mentioned that this work could also be situated in Section 7 focusing on cyclizations.



Scheme 30. Diels–Alder reaction of 1,3-cyclohexadiene with chalcones.

9. CONCLUSIONS

In comparison with more traditional metals, less toxic and cheaper aluminum encounters a growing success, especially in the context of greener catalysis. While investigated only since 1990s, chiral aluminum catalysts are increasingly applied to promote many types of enantioselective transformations. This review updates this field since 2015, demonstrating that asymmetric aluminum catalysis is booming. The diversity of asymmetric aluminum-catalyzed transformations recently reported, spanning from cyanations of carbonyl compounds, aldol reactions, reductions of ketones, kinetic resolutions, desymmetrizations and deracemizations among other reactions to more complex domino and tandem reactions, reflects that of chiral aluminum ligands employed to promote them, including salens, BINOL and VANOL derivatives, TADDOL-derived ligands, cinchona alkaloids, and *N,N'*-dioxides. For example in the last few years, was performed the first example of asymmetric formal [3+2] cycloaddition between three-membered carboxamides and alkynes promoted by a Al/Ni bimetallic catalyst derived from a TADDOL-derived chiral ligand, affording chiral cyclopentenyl carboxamides with up to 94% ee. Moreover, a related bimetallic catalyst allowed a novel asymmetric domino reaction of aryl nitriles with alkynes to be achieved with up to 98% ee, opening a route to chiral indenenes. An asymmetric aluminum-catalyzed tandem Wittig/cyanosilylation reaction of aldehydes with phosphorane and TMS-CN resulted in the formation of a wide range of chiral functionalized cyanohydrins with 95% ee by using a chiral salen ligand. Progress has also been made in the field of asymmetric cyanations of carbonyl compounds. For example, the cyanation of challenging dialkyl ketones was disclosed by using a chiral salen aluminum complex with 95% ee. Furthermore, an aluminum fluoride salen complex bearing an appended ammonium salt was used to promote the asymmetric carboxycyanation of aldehydes at as low as 0.1 mol% of catalyst loading by using either ethyl cyanofornate or less toxic and cheaper KCN as cyanide agent with respectively 97% and 95% ee. In another area, high ee values of 91% ee were described in desymmetrizations of *meso*-epoxides with AcBr by using an aluminum chloride salen complex. In the area of aldol condensations, a BINOL-derived Al/Zn heterobimetallic complex was employed with high enantioselectivity (90% ee) in the aldol reaction between acetophenone and aldehydes. Even higher ee values (98% ee) were reported in the aldol reaction of cyclohexanone with benzaldehydes performed in water in the presence of a novel chiral cinchona alkaloid-tethered aluminum phosphonate complex. Borohydride reductions of 2-pyridine ketones, various five-membered heterocyclic ketones and acetophenone catalyzed by a chiral aluminum complex of a BINOL derivative were disclosed with up to 99% ee, while a VANOL-derived aluminum complex allowed comparable ee values to be achieved in asymmetric Meerwein–Ponndorf–Verley reductions of ketones. In addition, a highly enantioselective aza-Michael addition of tetrafluorophthalimide to α,β -unsaturated ketones was achieved under catalysis with a chiral dinuclear salen aluminum complex with up to 97% ee. A chiral H_8 -BINOL-derived aluminum complex was found capable of promoting enantioselective vinylation of aldehydes with 89% ee. Even higher ee values (up to 93% ee) were reported in enantioselective reactions of aliphatic aldehydes with different types of α -bromo carbonyl compounds catalyzed by a chiral aluminum salen complex. Another type of ligands, such as chiral *N,N'*-dioxides, were applied in asymmetric aluminum-catalyzed acyloin rearrangements of cyclic α -ketols and α -hydroxy aldehydes with up to 92% ee. In spite of these good results, further efforts are awaited with the involvement of other types of transformations as well as that of novel chiral catalysts to make aluminum a green competing metal.

AUTHOR'S CONTRIBUTIONS

The author confirms sole responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

LIST OF ABBREVIATIONS

Ar: aryl

BINOL: 1,1'-bi-2-naphthol

Bn: benzyl

Boc: *tert*-butoxycarbonyl

cod: cyclooctadiene

Cp: cyclopentadienyl

Cy: cyclohexyl

de: diastereomeric excess

DMF: dimethylformamide

ee: enantiomeric excess

EWG: electron-withdrawing

Hept: heptyl

Hex: hexyl

IBAO: isobutylaluminumoxane

MS: molecular sieves

Naph: naphthyl

Pent: pentyl

Pin: pinacolato

PPN: bis(triphenylphosphine)iminium

r.t.: room temperature

TBS: *tert*-butyldimethylsilyl

TEMPO: 2,2,6,6-tetramethyl-1-piperidinyloxy

Tf: trifluoromethane sulfonyl

THF: tetrahydrofuran

Tipp: (2,4,6-triisopropyl)phenyl

TMS: trimethylsilyl

Tol: tolyl

VANOL: 3,3'-diphenyl-2,2'-bi-(1-naphthol)

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

This work was supported by the National Centre for Scientific Research: CNRS.

REFERENCES

-
- [1] Pellissier, H. Recent developments in enantioselective scandium-catalyzed transformations. *Chemistry*, **2024**, *6*, 98–152.
- [2] Arai, T.; Bougauchi, M.; Sasai, H.; Shibasaki, M. Catalytic asymmetric synthesis of α -hydroxy phosphonates using the Al-Li-BINOL complex. *J. Org. Chem.*, **1996**, *61*, 2926–2927.
- [3] Pellissier, H. TADDOL-derived phosphorus ligands in asymmetric catalysis. *Coord. Chem. Rev.*, **2023**, *482*, 215079.
- [4] Xie, M.; Feng, X. In: RSC Green Chemistry Series, North, M., Ed., RSC: Cambridge, **2016**, Vol. 39, pp 165–211.
- [5] Wilkins, L. C.; Melen, R. L. Enantioselective Main Group Catalysis: Modern Catalysts for Organic Transformations. *Coord. Chem. Rev.*, **2016**, *324*, 123–139.
- [6] Gualandi, A.; Calogero, F.; Potenti, S.; Cozzi, P. G. Al(Salen) Metal Complexes in Stereoselective Catalysis. *Molecules*, **2019**, *24*, 1716–1739.
- [7] Luan, Y.-X.; Ye, M. Ligand-ligated Ni–Al bimetallic catalysis for C–H and C–C bond activation. *Chem. Commun.*, **2022**, *58*, 12260–12273.
- [8] (a) Maruoka, K.; Yamamoto, H. Organoaluminums in organic synthesis. *Tetrahedron*, 1988, *44*, 5001–5032. (b) Wang, C.; Xi, Z. Co-operative effect of Lewis acids with transition metals for organic synthesis. *Chem. Soc. Rev.*, **2007**, *36*, 1395–1406. (c) Uhl, W. Hydroalumination and hydrogallation of alkynes: New insights into the course of well-known reactions. *Coord. Chem. Rev.*, **2008**, *252*, 1540–1563. (d) Woodward, S.; Dagorne, S. Modern Organoaluminum Reagents: Preparation, Structure, Reactivity and Use; Springer: Heidelberg, **2013**, Vol 41.
- [9] Pramanik, M.; Guerzoni, M. G.; Richards, E.; Melen, R. L. Recent Advances in Asymmetric Catalysis Using p-Block Elements. *Angew. Chem., Int. Ed.*, **2024**, *63*, e202316461.
- [10] (a) Posner, G. H. Multicomponent one-pot annulations forming 3 to 6 bonds. *Chem. Rev.*, **1986**, *86*, 831–844. (b) Tietze, L. F.; Beifuss, U. Sequential Transformations in Organic Chemistry: A Synthetic Strategy with a Future. *Angew. Chem., Int. Ed.*, **1993**, *32*, 131–163 (c) Tietze, L. F. Domino Reactions in Organic Synthesis. *Chem. Rev.*, **1996**, *96*, 115–136. (d) Dalko, P. I.; Moisan, L. In the Golden Age of Organocatalysis. *Angew. Chem., Int. Ed.*, **2004**, *43*, 5138–5175. (e) Ramon, D. J.; Yus, M. Asymmetric Multicomponent Reactions (AMCRs): The New Frontier. *Angew. Chem., Int. Ed.*, **2005**, *44*, 1602–1634. (f) Zhu, J.; Bienaymé, H. Multicomponent Reactions, Wiley-VCH: Weinheim, **2005**. (g) Tietze, L. F.; Brasche, G.; Gericke, K. Domino Reactions in Organic Synthesis, Wiley-VCH: Weinheim, **2006**. (h) Pellissier, H. Asymmetric domino reactions. Part B: Reactions based on the use of chiral catalysts and biocatalysts. *Tetrahedron*, **2006**, *62*, 2143–2173. (i) Pellissier, H. Asymmetric domino reactions. Part A: Reactions based on the use of chiral auxiliaries. *Tetrahedron*, **2006**, *62*, 1619–1665. (j) Enders, D.; Grondal, C.; Hüttl, M. R. M. Asymmetric organocatalytic domino reactions. *Angew. Chem., Int. Ed.*, **2007**, *46*,

1570–1581. (k) Guillena, G.; Ramon, D. J.; Yus, M. Organocatalytic enantioselective multicomponent reactions (OEMCRs). *Tetrahedron: Asymmetry*, **2007**, *18*, 693–700. (l) Touré, B. B.; Hall, D. G. Natural Product Synthesis Using Multicomponent Reaction Strategies. *Chem. Rev.*, **2009**, *109*, 4439–4486. (m) Orru, R. V. A.; Ruijter, E. Synthesis of Heterocycles via Multicomponent Reactions, Topics in Heterocyclic Chemistry, Vols. I and II, Springer: Berlin, **2010**. (n) Pellissier, H. Recent Developments in Asymmetric Organocatalytic Domino Reactions. *Adv. Synth. Catal.*, **2012**, *354*, 237–294. (o) Clavier, H.; Pellissier, H. Recent Developments in Enantioselective Metal-Catalyzed Domino Reactions. *Adv. Synth. Catal.*, **2012**, *354*, 3347–3403. (p) Pellissier, H. Stereocontrolled Domino Reactions. *Chem. Rev.*, **2013**, *113*, 442–524. (q) Pellissier, H. Asymmetric Domino Reactions, Royal Society of Chemistry: Cambridge, **2013**. (r) Tietze, L. F. *Domino Reactions - Concepts for Efficient Organic Synthesis*, Wiley-VCH: Weinheim, **2014**. (s) J. Zhu, Q. Wang, M. Wang, Multicomponent Reactions in Organic Synthesis, Wiley: Weinheim, **2014**. (t) Herrera, R. P.; Marques-Lopez, E. Multicomponent Reactions: Concepts and Applications for Design and Synthesis, Wiley: Weinheim, **2015**. (u) Snyder, S. A. Science of Synthesis. Applications of Domino Transformations in Organic Synthesis, Thieme Verlag: Stuttgart, **2016**, Vols 1-2. (v) Pellissier, H. Recent Developments in Enantioselective Metal-Catalyzed Domino Reactions. *Adv. Synth. Catal.*, **2016**, *358*, 2194–2259. (w) Pellissier, H. Recent developments in enantioselective metal-catalyzed domino reactions. *Adv. Synth. Catal.*, **2019**, *361*, 1733–1755. (x) Pellissier, H. Asymmetric Metal Catalysis in Enantioselective Domino Reactions, Wiley: Weinheim, **2019**. (y) Pellissier, H. The Use of Domino Reactions for the Synthesis of Chiral Rings. *Synthesis*, **2020**, *52*, 3837–3854. (z) Pellissier, H. Recent Developments in Enantioselective Domino Reactions. Part A: Noble Metal Catalysts. *Adv. Synth. Catal.*, **2023**, *365*, 620–681. (aa) Pellissier, H. Recent Developments in Enantioselective Domino Reactions. Part B: First Row Metal Catalysts. *Adv. Synth. Catal.*, **2023**, *365*, 768–819.

[11] Wang, S.-X.; Wang, M.-X.; Wang, D.-X.; Zhu, J. Chiral Salen–Aluminum Complex as a Catalyst for Enantioselective α -Addition of Isocyanides to Aldehydes: Asymmetric Synthesis of 2-(1-Hydroxyalkyl)-5-aminoxazoles. *Org. Lett.*, **2007**, *9*, 3615–3618.

[12] Wang, S.-X.; Wang, M.-X.; Wang, D.-X.; Zhu, J. Catalytic Enantioselective Passerini Three-Component Reaction. *Angew. Chem., Int. Ed.*, **2008**, *47*, 388–391.

[13] Yue, T.; Wang, M.-X.; Wang, D.-X.; Zhu, J. Asymmetric Synthesis of 5-(1-Hydroxyalkyl)tetrazoles by Catalytic Enantioselective Passerini-Type Reactions. *Angew. Chem., Int. Ed.*, **2008**, *47*, 9454–9457.

[14] Xie, G.; Feng, D.; Ma, X. 9-Amino(9-deoxy)epi-cinchona alkaloid-tethered aluminium phosphonate architectures for heterogeneous cooperative catalysis: asymmetric aldol and double-Michael cascade reaction. *Mol. Catal.*, **2017**, *434*, 86–95.

[15] Liu, Q.-S.; Wang, D.-Y.; Yang, Z.-J.; Luan, Y.-X.; Yang, J.-F.; Li, J.-F.; Pu, Y.-G.; Ye, M. Ni–Al Bimetallic Catalyzed Enantioselective Cycloaddition of Cyclopropyl Carboxamide with Alkyne. *J. Am. Chem. Soc.*, **2017**, *139*, 18150–18153.

[16] Zhang, T.; Luan, Y.-X.; Zheng, S.-J.; Peng, Q.; Ye, M. Chiral Aluminum Complex Controls Enantioselective Nickel-Catalyzed Synthesis of Indenes: C–CN Bond Activation. *Angew. Chem., Int. Ed.*, **2020**, *59*, 7439–7443.

[17] (a) Ho, T.-L. *Tandem Organic Reactions*; Wiley: New York; **1992**. (b) Bunce, R. A. Recent advances in the use of tandem reactions for organic synthesis. *Tetrahedron*, **1995**, *51*, 13103–13159. (c) Padwa, A.; Weingarten, M. D. Cascade Processes of Metallo Carbenoids. *Chem. Rev.*, **1996**, *96*, 223–270. (d) Denmark, S. E.; Thorarensen, A. Tandem [4+2]/[3+2] Cycloadditions of Nitroalkenes. *Chem. Rev.*, **1996**, *96*, 137–166. (e) Hulme, C.; Gore, V. "Multi-component reactions: emerging chemistry in drug discovery" from xylocain to crivivan'. *Curr. Med. Chem.*, **2003**, *10*, 51–80. (f) Tietze, L. F.; Rackelmann, N. Domino reactions in the synthesis of heterocyclic natural products and analogs. *Pure Appl. Chem.*, **2004**, *76*, 1967–1983. (g) Fogg, D. E.; dos Santos, E. N. Tandem catalysis: a taxonomy and illustrative review. *Coord. Chem. Rev.*, **2004**, *248*, 2365–2379. (h) Wasilke, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. Concurrent Tandem Catalysis. *Chem. Rev.*, **2005**, *105*, 1001–1020. (i) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. Cascade Reactions in Total Synthesis. *Angew. Chem., Int. Ed.*, **2006**, *45*, 7134–7186. (j) Chapman, C. J.; Frost, C. G. Tandem and domino catalytic strategies for enantioselective synthesis. *Synthesis*, **2007**, 1–21. (k) Padwa, A.; Bur, S. K. The Domino Way to Heterocycles. *Tetrahedron*, **2007**, *63*, 5341–5378. (l) D'Souza, D. M.; Müller, T. J. J. Multi-component syntheses of heterocycles by transition-metal catalysis. *Chem. Soc. Rev.*, **2007**, *36*, 1095–1108. (m) Alba, A.-N.; Companyo, X.; Viciano, M.; Rios, R. Organocatalytic Domino Reactions. *Curr. Org. Chem.*, **2009**, *13*, 1432–1474. (n) *Chem. Soc. Rev.*, **2009**, Special Issue on Rapid formation of molecular complexity in organic synthesis. (o) Nicolaou, K. C.; Chen, J. S. The art of total synthesis through cascade reactions. *Chem. Soc. Rev.*, **2009**, *38*, 2993–3009. (p) Ruiz, M.; Lopez-Alvarado, P.; Giorgi, G.; Menéndez, J. C. Domino reactions for the synthesis of bridged bicyclic frameworks: fast access to bicyclo[n.3.1]alkanes. *Chem. Soc. Rev.*, **2011**, *40*, 3445–3454. (q) De Graaff, C.; Ruijter, E.; Orru, R. V. A. Recent developments in asymmetric multicomponent reactions. *Chem. Soc. Rev.*, **2012**, *41*, 3969–4009. (r) Pellissier, H. Recent Developments in Enantioselective Multicatalysed Tandem Reactions. *Tetrahedron*, **2013**, *69*, 7171–7210. (s) Pellissier, H. *Enantioselective Multicatalysed Tandem Reactions*, Royal Society of Chemistry: Cambridge, **2014**. (t) Ardhean, R.; Caputo, D. F. J.; Morrow, S. M.; Shi, H.; Xiong, Y.; Anderson, E. A. Cascade polycyclizations in natural product synthesis. *Chem. Soc. Rev.*, **2016**, *45*, 1557–1569. (u) Pellissier, H. Enantioselective Nickel-Catalyzed Domino and Tandem Processes. *Curr. Org. Chem.*, **2016**, *20*, 234–265. (v) Hayashi, Y. Pot economy and one-pot synthesis. *Chem. Sci.*, **2016**, *7*, 866–880. (w) Pellissier, H. Recent Developments in Enantioselective Multicatalyzed Tandem Reactions. *Adv. Synth. Catal.*, **2020**, *362*, 2289–2325.

[18] Zeng, X.-P.; Cao, Z.-Y.; Wang, X.; Chen, L.; Zhou, F.; Zhu, F.; Wang, C.-H.; Zhou, J. Activation of Chiral (Salen)AlCl Complex by Phosphorane for Highly Enantioselective Cyanosilylation of Ketones and Enones. *J. Am. Chem. Soc.*, **2016**, *138*, 416–425.

[19] Stegbauer, S.; Jandl, C.; Bach, T. Chiral Lewis acid catalysis in a visible light-triggered cycloaddition/rearrangement cascade. *Chem. Sci.*, **2022**, *13*, 11856–11862.

[20] (a) Ramon, D. J.; Yus, M. In the Arena of Enantioselective Synthesis, Titanium Complexes Wear the Laurel Wreath. *Chem. Rev.*, **2006**, *106*, 2126–2208. (b) Yu, Y.; Ding, K.; Chen, G. In: Yamamoto, H.; Ishihara, K. *Acid Catalysis in Modern Organic Synthesis*; Wiley-VCH: Weinheim, **2008**; Chapter 14, p 721. (c) Khan, N. H.; Kureshi, R. I.; Abdi, S. H. R.; Agrawal, S.; Jasra, R. V. Metal catalyzed asymmetric cyanation reactions. *Coord. Chem. Rev.*, **2008**, *252*, 593–623. (d) North, M.; Usanov, D. L.; Young, C. Lewis Acid Catalyzed Asymmetric Cyanohydrin Synthesis. *Chem. Rev.*, **2008**, *108*, 5146–5226. (e) Wang, W.; Liu, W.; Lin, L.; Feng, X. Recent Progress in the Chemically Catalyzed Enantioselective Synthesis of Cyanohydrins. *Eur. J. Org. Chem.*, **2010**, 4751–4769. (f) North, M. A Bimetallic Titanium Catalyst

for the Enantioselective Cyanation of Aldehydes Based on Cooperative Catalysis. *Angew. Chem., Int. Ed.*, **2010**, *49*, 8079–8081. (g) Pellissier, H. Enantioselective Titanium-Catalyzed Cyanation Reactions of Carbonyl Compounds. *Adv. Synth. Catal.*, **2015**, *357*, 857–882.

[21] Sigman, M. S.; Jacobsen, E. N. Enantioselective Addition of Hydrogen Cyanide to Imines Catalyzed by a Chiral (Salen)Al(III) Complex. *J. Am. Chem. Soc.*, **1998**, *120*, 5315–5316.

[22] Gregory, R. J. H. Cyanohydrins in Nature and the Laboratory: Biology, Preparations, and Synthetic Applications. *Chem. Rev.*, **1999**, *99*, 3649–3682.

[23] Brodbeck, D.; Broghammer, F.; Meisner, J.; Klepp, J.; Garnier, D.; Frey, W.; Kästner, J.; Peters, R. An Aluminum Fluoride Complex with an Appended Ammonium Salt as an Exceptionally Active Cooperative Catalyst for the Asymmetric Carboxycyanation of Aldehydes. *Angew. Chem., Int. Ed.*, **2017**, *56*, 4056–4060.

[24] Brodbeck, D.; Alvarez-Barcia, S.; Meisner, J.; Broghammer, F.; Klepp, J.; Garnier, D.; Frey, W.; Kästner, J.; Peters, R. Asymmetric Carboxycyanation of Aldehydes by Cooperative AlF/Onium Salt Catalysts: from Cyanofornate to KCN as Cyanide Source. *Chem. Eur. J.*, **2019**, *25*, 1515–1524.

[25] (a) Hoveyda, A. H.; Didiuk, M. T. *Curr. Org. Chem.*, **1998**, *2*, 489–526. (b) Cook, G. R. *Curr. Org. Chem.*, **2000**, *4*, 869–885. (c) Keith, M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.*, **2001**, *343*, 5–26. (d) Robinson, D. E. J. E.; Bull, S. D. *Tetrahedron: Asymmetry*, **2003**, *14*, 1407–1446. (e) Jarvo, E. R.; Miller, S. J. In: Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis, Supplement*; Springer, Berlin, **2004**, pp. 189–206. (f) Breuer, M.; Ditrach, K.; Habicher, T.; Hauer, B.; Kessler, M.; Stürmer, R.; Zelinski, T. *Angew. Chem., Int. Ed.*, **2004**, *43*, 788–824. (g) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.*, **2005**, *44*, 3974–4001. (h) Fogassy, E.; Nogradi, M.; Kozma, D.; Egri, G.; Palovics, E.; Kiss, V. *Org. Biomol. Chem.*, **2006**, *4*, 3011–3030. (i) Wurz, R. P. *Chem. Rev.*, **2007**, *107*, 5570–5595. (j) Pellissier, H. *Adv. Synth. Catal.*, **2011**, *353*, 1613–1666. (k) Pellissier, H. In: Todd, M. *Separation of Enantiomers, Synthetic Methods*; Wiley-VCH, Weinheim, **2014**. (l) Petersen, K. S. *Asian J. Org. Chem.*, **2016**, *5*, 308–320; (m) Pellissier, H. *Tetrahedron*, **2018**, *74*, 3459–3468. (n) Pellissier, H. In: Bryliakov, K. P. *Frontiers of Green Catalytic Selective Oxidations*; Springer, Heidelberg, **2019**.

[26] (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. Asymmetric catalysis with water: efficient kinetic resolution of terminal epoxides by means of catalytic hydrolysis. *Science*, **1997**, *277*, 936–938. (b) Schneider, C. Synthesis of 1,2-Difunctionalized Fine Chemicals through Catalytic, Enantioselective Ring-Opening Reactions of Epoxides. *Synthesis*, **2006**, *23*, 3919–3944. (c) Pastor, I. M.; Yus, M. Asymmetric Ring Opening of Epoxides. *Curr. Org. Chem.*, **2005**, *9*, 1–29.

[27] North, M.; Quek, S. C. Z.; Pridmore, N. E.; Whitwood, A. C.; Wu, X. Aluminum(salen) complexes as catalysts for the kinetic resolution of terminal epoxides via CO₂ coupling. *ACSCatal.*, **2015**, *5*, 3398–3402.

[28] Itoh, H.; Maeda, H.; Yamada, S.; Hori, Y.; Mino, T.; Sakamoto, M. BINOL-Al catalyzed kinetic resolution of citronellal analogues: synthesis of a variety of fragrances. *Tetrahedron: Asymmetry*, **2016**, *27*, 698–705.

[29] Broghammer, F.; Brodbeck, D.; Junge, T.; Peters, R. Cooperative Lewis acid–onium salt catalysis as tool for the desymmetrization of meso-epoxides. *Chem. Commun.*, **2017**, *53*, 1156–1159.

[30] (a) Li, J.; Liu, Y.; Ren, W.-M.; Lu, X.-B. Asymmetric Alternating Copolymerization of Meso-epoxides and Cyclic Anhydrides: Efficient Access to Enantiopure Polyesters. *J. Am. Chem. Soc.*, **2016**, *138*, 11493–11496. (b) Ren, B.-H.; Teng, Y.-Q.; Wang, S.-N.; Wang, S.; Liu, Y.; Ren, W.-M.; Lu, X.-B. Mechanistic Basis for the High Enantioselectivity and Activity in the Multichiral Bimetallic Complex-Mediated Enantioselective Copolymerization of meso-Epoxides. *ACS Catal.*, **2022**, *12*, 12268–12280.

[31] Li, Yi-Ning; Liu, Y.; Yang, H.-H.; Zhang, W.-F.; Lu, X.-B. Intramolecular Partners in Asymmetric Catalysis Copolymerization: Highly Enantioselective and Controllable at Enhanced Temperatures and Low Loadings. *Angew. Chem., Int. Ed.*, **2022**, *61*, e202202585.

[32] Li, Y.-N.; Yang, H.-H.; Lu, X.-B. Intramolecular synergistic catalysis for asymmetric alternating copolymerization of CO₂ and meso-epoxides. *J. Polym. Sci.*, **2022**, *60*, 2078–2085.

[33] (a) He, G.-H.; Ren, B.-H.; Chen, S.-Y.; Liu, Y.; Lu, X.-B. *Angew. Chem., Int. Ed.*, **2021**, *60*, 5994–6002. (b) Li, J.; Ren, B.-H.; Chen, S.-Y.; He, G.-H.; Liu, Y.; Ren, W.-M.; Zhou, H.; Lu, X.-B. Development of Highly Enantioselective Catalysts for Asymmetric Copolymerization of meso-Epoxides and Cyclic Anhydrides: Subtle Modification Resulting in Superior Enantioselectivity. *ACS Catal.*, **2019**, *9*, 1915–1922.

[34] Onneken, C.; Morack, T.; Soika, J.; Sokolova, O.; Niemeyer, N.; Mück-Lichtenfeld, C.; Daniliuc, C. G.; Neugebauer, J.; Gilmour, R. Light-enabled deracemization of cyclopropanes by Al-salen photocatalysis. *Nature*, **2023**, *621*, 753–759.

[35] Li, X.; Zhang, L.; Xiao, Y.-H.; Guo, Q.-P.; Da, C. S.; Li, H.; Liu, X.; Ma, X.; Ma, Y. Direct asymmetric aldol reaction of acetophenones with aromatic aldehydes catalyzed by chiral Al/Zn heterobimetallic compounds. *Russ. J. Gen. Chem.*, **2016**, *86*, 1922–1930.

[36] Lebedev, Y.; Polishchuk, I.; Maity, B.; Veloso Guerreiro, M. D.; Cavallo, L.; Rueping, M. Asymmetric Hydroboration of Heteroaryl Ketones by Aluminum Catalysis. *J. Am. Chem. Soc.*, **2019**, *141*, 19415–19423.

[37] Zheng, L.; Yin, X.; Mohammadlou, A.; Sullivan, R. P.; Guan, Y.; Staples, R.; Wulff, W. D. Asymmetric Catalytic Meerwein–Ponndorf–Verley Reduction of Ketones with Aluminum(III)-VANOL Catalysts. *ACSCatal.*, **2020**, *10*, 7188–7194.

[38] Titze, M.; Heitkämper, J.; Junge, T.; Kästner, J.; Peters, R. Highly Active Cooperative Lewis Acid–Ammonium Salt Catalyst for the Enantioselective Hydroboration of Ketones. *Angew. Chem., Int. Ed.*, **2021**, *60*, 5544–5553.

-
- [39] Itoh, H.; Maeda, H.; Yamada, S.; Hori, Y.; Mino, T.; Sakamoto, M. BINOL-Al catalysed asymmetric cyclization and amplification: preparation of optically active menthol analogs. *Org. Biomol. Chem.*, **2015**, *13*, 5817–5825.
- [40] Wang, Y.-X.; Qi, S.-L.; Luan, Y.-X.; Han, X.-W.; Wang, S.; Chen, H.; Ye, M. Enantioselective Ni–Al Bimetallic Catalyzed *exo*-Selective C–H Cyclization of Imidazoles with Alkenes. *J. Am. Chem. Soc.*, **2018**, *140*, 5360–5364.
- [41] Li, J.-F.; Xu, W.-W.; Wang, R.-H.; Li, Y.; Yin, G.; Ye, M. Construction 7-membered ring via Ni–Al bimetal-enabled C–H cyclization for synthesis of tricyclic imidazoles. *Nature Com.*, **2021**, *12*, 3070–3079.
- [42] Myers, J. K.; Jacobsen, E. N. Asymmetric Synthesis of β -Amino Acid Derivatives via Catalytic Conjugate Addition of Hydrazoic Acid to Unsaturated Imides. *J. Am. Chem. Soc.*, **1999**, *121*, 8959–8960.
- [43] Avidan-Shlomovich, S.; Ghosh, H.; Szpilman, A. M. Synthetic and Mechanistic Study of the Catalytic Enantioselective Preparation of Primary β -Amino Ketones from Enones and a Fluorinated Gabriel Reagent. *ACSCatal.*, **2015**, *5*, 336–342.
- [44] Adate, P. A.; Matsunaga, T.; Shin, H.; Harada, T. Chiral Aluminum Catalyzed Enantioselective Vinylation of Aldehydes. *Adv. Synth. Catal.*, **2016**, *358*, 3688–3693.
- [45] Gualandi, A.; Marchini, M.; Mengozzi, L.; Tesfay Kidanu, H.; Franc, A.; Ceroni, P.; Cozzi, P. G. Aluminum(III) Salen Complexes as Active Photoredox Catalysts. *Eur. J. Org. Chem.*, **2020**, 1486–1490.
- [46] Dai, L.; Li, X.; Zeng, Z.; Dong, S.; Zhou, Y.; Liu, X.; Feng, X. Catalytic Asymmetric Acyloin Rearrangements of α -Ketols, α -Hydroxy Aldehydes, and α -Iminols by *N,N'*-Dioxide–Metal Complexes. *Org. Lett.*, **2020**, *22*, 5041–5045.
- [47] Homer, J. A.; De Silvestro, I.; Matheson, E. J.; Stuart, J. T.; Lawrence, A. L. Enantioselective *para*-Claisen Rearrangement for the Synthesis of *Illicium*-Derived Prenylated Phenylpropanoids. *Org. Lett.*, **2021**, *23*, 3248–3252.
- [48] Dissanayake, D.; Forsyth, C.; Vidovic, D. Synthesis, characterisation and reactivity studies of chiral β -diketiminato-like supported aluminium Lewis acid complexes towards difficult Diels Alder cycloadditions. *Dalton Trans.*, **2023**, *52*, 4063–4076.