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# Recent developments in enantioselective titanium-catalyzed transformations

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## **1. Introduction**

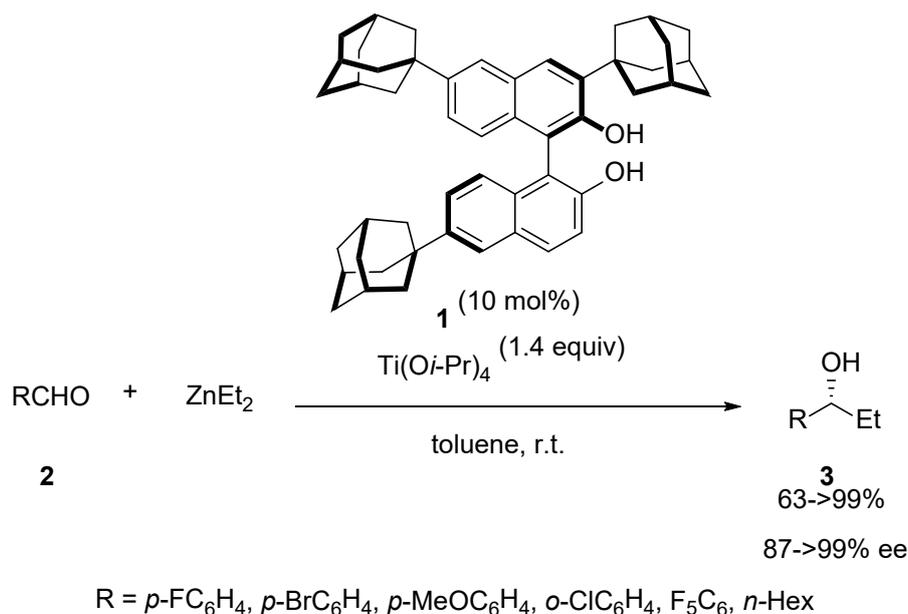
In comparison with most transition metals employed in catalysis [1], titanium catalysts present the advantages to be cheaper and non-toxic, which have triggered the development of a wide range of more economic and ecologic titanium-mediated transformations as well as the

use of titanium for medical uses, such as prosthesis composition [2]. The great interest in titanium might also be related to the fact that titanium complexes are of high abundance and exhibit a diverse chemical reactivity, making them ones of the most useful Lewis acids in catalysis. These green catalysts have been proven to be highly efficient to promote many types of organic transformations spanning from basic ones, such as oxidations, nucleophilic additions to carbonyl compounds, reductions, cycloadditions, ring-opening reactions among others to more modern methodologies including domino reactions. Especially, the excellent capability of various types of chiral titanium catalysts to control the stereochemistry is related to their rich coordination chemistry and facile modification of titanium Lewis acid center by structurally modular ligands. An increasing and amazing number of highly enantioselective reactions of all types have already been described under environmentally friendly conditions, including asymmetric oxidations, reductions, carbon–carbon bond formations, carbon–heteroatoms bond formations, as well as carbon–hydrogen functionalizations. The goal of this review is to update the field of enantioselective titanium-catalyzed transformations published since the beginning of 2015, since this field was most recently reviewed in 2016 by a book covering the literature up to the end of 2014 [3], and earlier by several reports [2c-d,f-g]. The review is divided into eight parts, dealing successively with enantioselective titanium-catalyzed 1,2-additions of carbon nucleophiles to carbonyl compounds, sulfoxidations, epoxidations, reduction reactions, domino reactions, cycloadditions, dihalogenations of alkenes, and miscellaneous reactions.

## **2. Enantioselective titanium-catalyzed 1,2-additions of carbon nucleophiles to carbonyl compounds**

### **2.1. Alkylation of aldehydes**

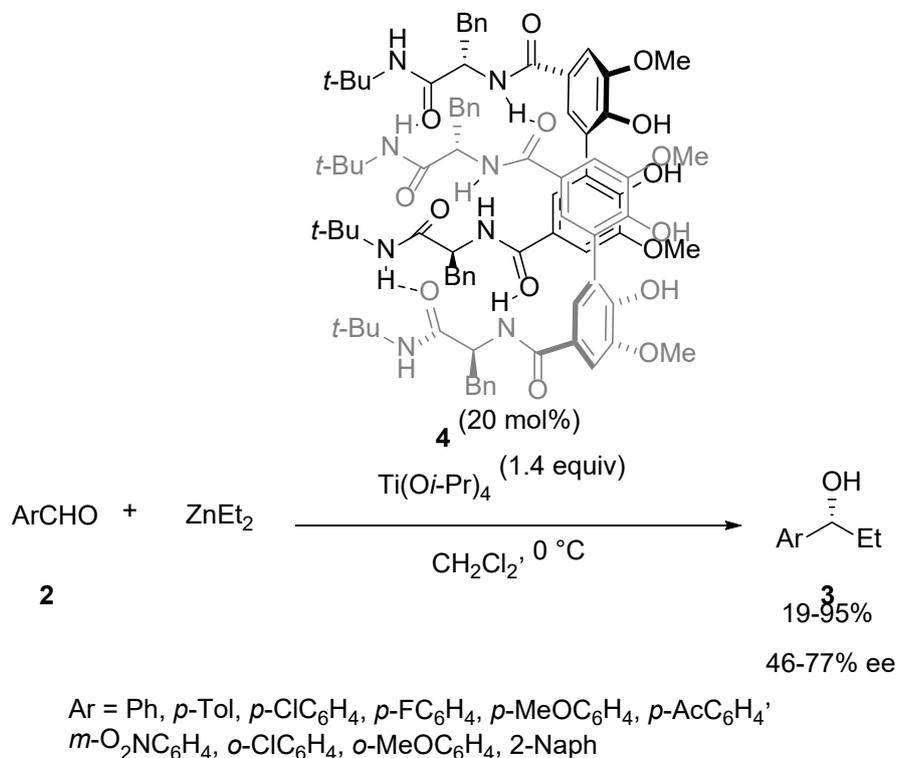
The formation of a carbon–carbon bond via nucleophilic addition of an organometallic reagent to a carbonyl compound constitutes a basic transformation in organic chemistry, leading to alcohols [4]. These additions of organozinc, magnesium, titanium, lithium, aluminum, boron and zirconium species to aldehydes and ketones can be promoted by titanium complexes, evolving through the transmetallation of organometallic reagents into alkyltitanium complexes. Since the first highly enantioselective titanium-promoted addition of diethylzinc to benzaldehyde reported in 1989 by Ohno and Yoshioka [5], a range of asymmetric titanium-promoted additions of dialkylzinc reagents to aldehydes and ketones have been successfully developed [4i,6]. Among them, many have involved BINOL-derived ligands [7], allowing moderate to excellent enantioselectivities of up to 99% ee to be achieved, by using mostly superstoichiometric amounts of  $\text{Ti}(\text{O}i\text{-Pr})_4$  [8]. In a more recent example, Iglesias and Sanchez designed novel hindered BINOL ligands to be investigated in the asymmetric titanium-catalyzed ethylation of aldehydes with  $\text{ZnEt}_2$  [9]. Among several chiral BINOL derivatives bearing bulky substituents, congested ligand **1** exhibiting tertiary adamantyl groups at the 3, 6 and 6' positions of the BINOL moiety was selected as most efficient to promote in combination with  $\text{Ti}(\text{O}i\text{-Pr})_4$  the condensation of  $\text{ZnEt}_2$  to various aldehydes **2**. The reaction was performed at room temperature in toluene as solvent in the presence of only 10 mol% of ligand **1** combined with 1.4 equivalent of the titanium complex. As shown in Scheme 1, aromatic as well as aliphatic aldehydes were compatible, leading to the corresponding chiral alcohols **3** in good to quantitative yields (63->99%) and uniformly high enantioselectivities (87->99% ee).



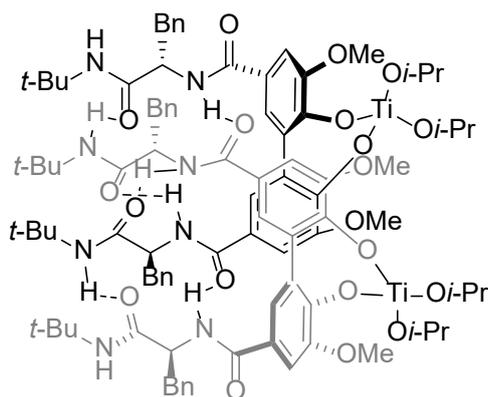
**Scheme 1.** Ethylation of aromatic/aliphatic aldehydes with  $\text{ZnEt}_2$  in the presence of BINOL-derived ligand **1** [9].

In 2019, Trapp and Scholtes described the synthesis of a novel type of biphenyl-based ligands exhibiting chiral amino acid-derived diamide substituents at the 5,5'-positions [10]. The latter formed dimeric supramolecular structures stabilized by intermolecular hydrogen bonding, providing a diastereoselective interlocking of the interaction sites of the two biphenol units. The resulted axial chirality of these self assembled BIPOL-derived ligands was demonstrated through X-ray crystallography (Scheme 2). They were further investigated to promote titanium-catalyzed ethylation of aromatic aldehydes with  $\text{ZnEt}_2$  in the presence of  $\text{Ti(O}i\text{-Pr)}_4$ . Performed at 0 °C in dichloromethane as solvent in the presence of 20 mol% of ligand **4**, the addition of  $\text{ZnEt}_2$  to a series of aromatic aldehydes **2** led to the corresponding chiral alcohols **3** in low to excellent yields (19-95%) and moderate to good enantioselectivities (46-77% ee), as presented in Scheme 2. The enantioselectivity of the reaction was found dependent on the steric hindrance of the substrates. For example, the

reaction of *para*-substituted aldehydes generally provided higher enantioselectivities (62-77% ee) than that of *ortho*-substituted aldehydes (47-56% ee).

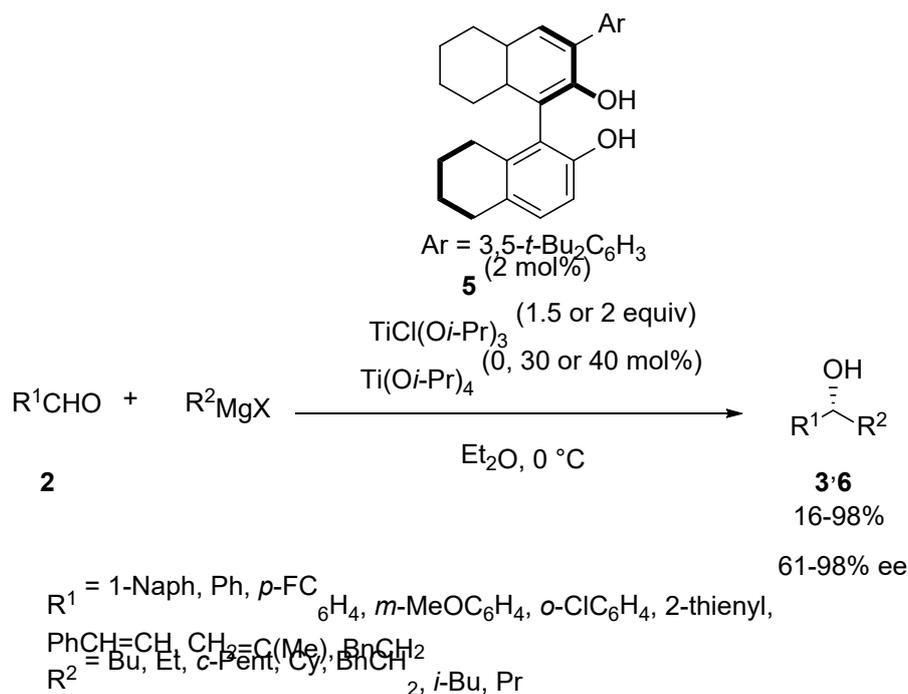


structure of in situ generated catalyst:



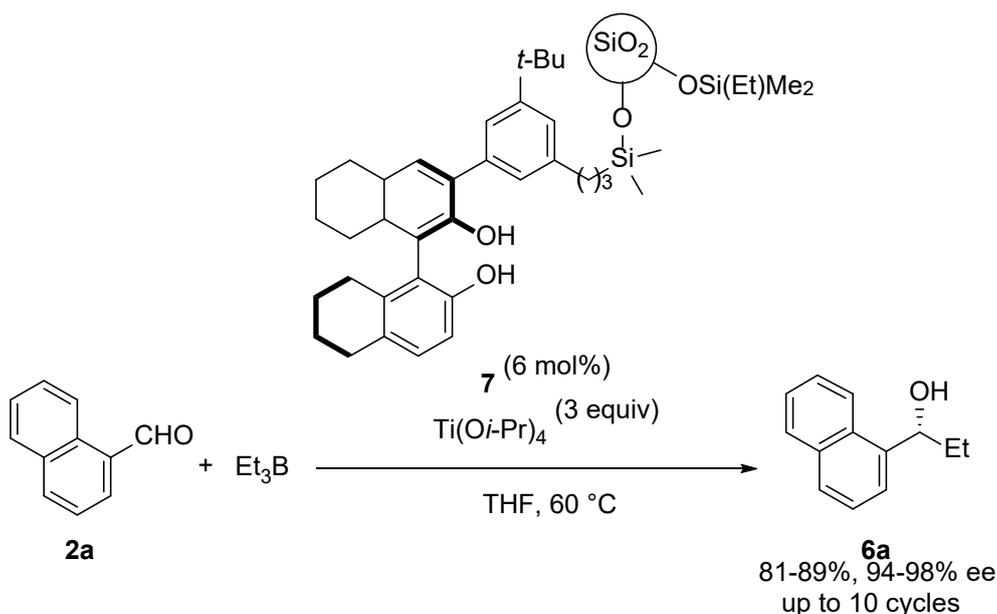
**Scheme 2.** Ethylation of aromatic aldehydes with ZnEt<sub>2</sub> in the presence of dimeric BIPOL-derived ligand **4** [10].

Along with organozinc species, Grignard reagents are among the cheapest organometallic reagents. Because of their high reactivity, direct enantioselective Grignard addition to aldehydes has been rarely disclosed [11]. Most of methodologies are based on previous transmetalation to form less reactive intermediates, such as  $\text{RTi}(\text{O}i\text{-Pr})_3$  in situ generated from  $\text{RMgX}$  and  $\text{Ti}(\text{O}i\text{-Pr})_4$ . One drawback of these processes is the required removal of co-produced magnesium salts through centrifugation before adding the aldehyde partner to the reaction mixture. In 2018, Harada et al. showed that it was possible to avoid this manipulation by generating the reactive alkyltitanium species from  $\text{TiCl}(\text{O}i\text{-Pr})_3$  instead of  $\text{Ti}(\text{O}i\text{-Pr})_4$  [12]. Indeed,  $\text{R}^2\text{MgX}$  was treated with  $\text{TiCl}(\text{O}i\text{-Pr})_3$  (1.5 or 2 equiv) to give a mixture of  $\text{R}^2\text{Ti}(\text{O}i\text{-Pr})_3$  and  $\text{MgXCl}$ . The titanium reagent was transferred together with the suspended magnesium salts to a  $\text{Et}_2\text{O}$  solution of aldehyde **2** at 0 °C containing 2 mol% of chiral H<sub>8</sub>-BINOL-derived ligand **5**. Under these conditions, the reaction afforded the corresponding chiral alcohols **3** and **6** in low to quantitative yields (16-98%) and good to excellent enantioselectivities (61-98% ee), as illustrated in Scheme 3. Notably, the reaction of aromatic aldehydes provided both higher yields (35-98% vs 16-82%) and enantioselectivities than aliphatic aldehydes (78-98% ee vs 61-93% ee).



**Scheme 3.** Alkylation of aldehydes with Grignard reagents in the presence of H<sub>8</sub>-BINOL-derived ligand **5** [12].

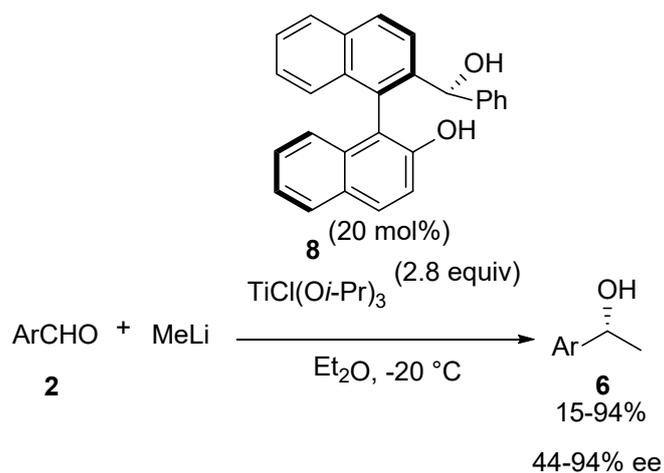
Alkylboranes also constitute potent alkylating reagents. It is only in 2008 that Harada and Ukon disclosed the first direct use of trialkylboranes without converting them into alkylmetallic species [13]. Later, the same authors developed a silica-supported H<sub>8</sub>-BINOL-derived ligand **7** to be applied in the alkylation of 1-naphthaldehyde **2a** with BEt<sub>3</sub> [14]. As shown in Scheme 4, the corresponding product **6a** was produced in both high yields and enantioselectivities (81-89%, 94-98% ee) even after recycling ligand **7** up to 10 cycles.



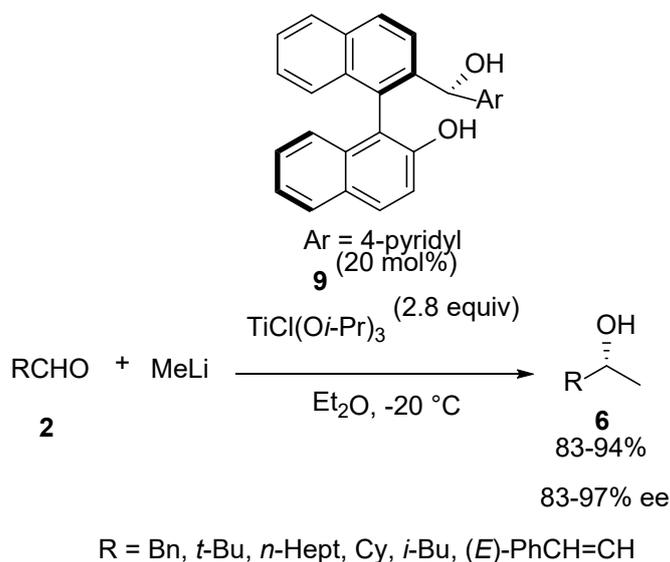
**Scheme 4.** Ethylation of 1-naphthaldehyde with  $\text{BEt}_3$  in the presence of silica-supported H<sub>8</sub>-BINOL-derived ligand **7** [14].

The asymmetric addition of organolithium compounds [15] to carbonyl compounds also constitute a direct route to chiral alcohols but has been much less studied related to their high reactivity. Early investigated by Seebach and later by Maddaluno [16], it is only in 2012 that Yus et al. reported the first catalytic system for the asymmetric alkylation of aldehydes with organolithium reagents performed in the presence of an excess of  $\text{Ti}(\text{O}i\text{-Pr})_4$  [17]. Importantly, this highly efficient procedure providing up to 96% ee allowed the direct use of these organometallic species without requiring salt-removal manipulations. With the aim of further improving these methodologies, Macia et al. reinvestigated their reaction conditions, in 2016 [18]. Indeed, these authors showed that the same reaction could be performed with only 2.8 equivalents of  $\text{TiCl}(\text{O}i\text{-Pr})_3$  instead of 6 equivalents of  $\text{Ti}(\text{O}i\text{-Pr})_4$  in diethylether as the solvent at  $-20\text{ }^\circ\text{C}$  instead of  $-40\text{ }^\circ\text{C}$  in the presence of the same quantity (20 mol%) of the same ligand Ph-BINMOL **8**. As illustrated in Scheme 5, a range of aromatic aldehydes **2**

reacted with methyllithium to give the corresponding chiral alcohols **6** in low to excellent yields (15-94%) and moderate to high enantioselectivities (44-94% ee). The reaction of *para*-substituted benzaldehydes provided uniformly high enantioselectivities (86-92% ee) while more sterically hindered *ortho*-anisaldehyde gave the lowest enantioselectivity (44% ee). Heteroaromatic aldehydes (Ar = 2-thienyl, 2-furyl) afforded the corresponding products in high enantioselectivities (84-93% ee) as well as 2-naphthaldehyde (90% ee). It must be noted that the process remarkably allowed the presence of halogen and nitrile functionalities on the aldehyde substrate in spite of the high reactivity of methyllithium. These mild conditions were also applicable to aliphatic aldehydes with moderate to high enantioselectivities (63-95% ee). It was found that even higher enantioselectivities were achieved by using closely related ligand Ar-BINMOL **9**. As shown in Scheme 5, a series of aliphatic aldehydes **2** reacted with methyllithium in the presence of 20 mol% of ligand **9** instead of **8** under the same reaction to give the corresponding alcohols **6** in both uniformly high yields (84-94%) and enantioselectivities (83-97% ee).



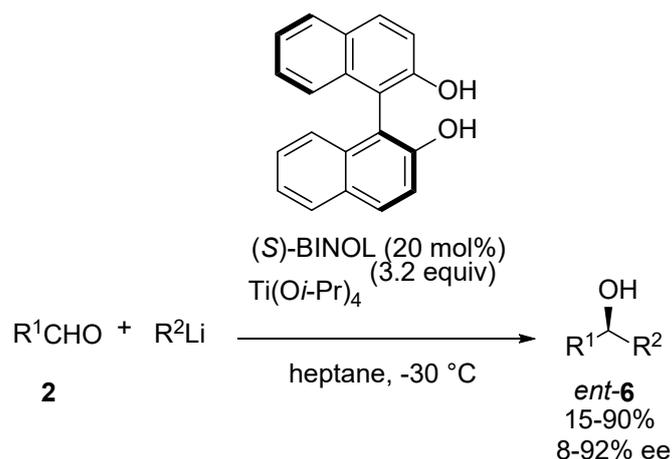
Ar = *p*-MeOC<sub>6</sub>H<sub>4</sub>, *p*-Tol, *o*-MeOC<sub>6</sub>H<sub>4</sub>, 2-Naph, 2-thienyl, 2-furyl,  
*p*-BrC<sub>6</sub>H<sub>4</sub>, *p*-ClC<sub>6</sub>H<sub>4</sub>, *p*-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, *p*-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>, *p*-NCC<sub>6</sub>H<sub>4</sub>



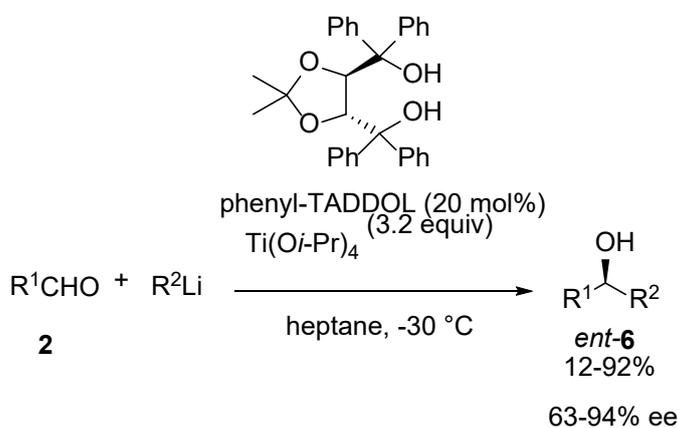
**Scheme 5.** Methylations of aromatic/aliphatic aldehydes with MeLi in the presence of Ar-BINMOL ligands **8** and **9** [18].

In the same year, Song and Huang also developed other simple one-step methodologies to synthesize chiral alcohols from catalytic asymmetric titanium-catalyzed addition of organolithium reagents to a range of aldehydes [19]. Performed at 30 °C, the processes employed 20 mol% of simple chiral ligands, such as (*S*)-BINOL and phenyl-TADDOL

ligand, combined with 3.2 equivalents of  $\text{Ti}(\text{O}i\text{-Pr})_4$  in heptane as the solvent. Under these mild reaction conditions, aromatic but also aliphatic aldehydes **2** reacted with various alkylolithiums to give the corresponding chiral alcohols *ent*-**6**. When using (*S*)-BINOL as ligand, these products were obtained in low to excellent yields (15-90%) and enantioselectivities (8-92% ee), as shown in Scheme 6. The reaction promoted with phenyl-TADDOL as ligand provided comparable yields (12-92%) albeit combined with good to high enantioselectivities (63-94% ee). In both cases of ligands, uniformly high enantioselectivities (84-92% ee with (*S*)-BINOL and 86-94% ee with phenyl-TADDOL) combined with good yields (68-90% with (*S*)-BINOL and 83-92% with phenyl-TADDOL) were obtained in the reaction of aromatic aldehydes with *n*-butyllithium. On the other hand, lower enantioselectivities (47-63% ee) were obtained in the reaction of an heteroaromatic aldehyde (R = 2-thienyl) and an aliphatic aldehyde (R = Cy, 52-68% ee). The latter aldehyde also provided low yields (12-15%). On the other hand, the use of *n*-hexyllithium provided high enantioselectivities (86-89% ee) while the lowest enantioselectivities (8-10% ee) were observed in the reaction of methylolithium with aromatic aldehydes performed in the presence of (*S*)-BINOL as ligand. The authors also showed that moderate yields (56-61%) and enantioselectivities (71-73% ee) were obtained in analogous arylations of aldehydes with phenyl lithium reagent.



$R^1 = \text{Ph, } p\text{-Tol, } p\text{-F}$   
 $\text{}_3\text{CC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, 2\text{-Naph,}$   
 2-thienyl,  $p\text{-Tol, } o\text{-MeOC}_6\text{H}_4, 2\text{-Naph, Cy, PhCH=CH}$   
 $R^2 = n\text{-Bu, Me, } n\text{-Hex}$

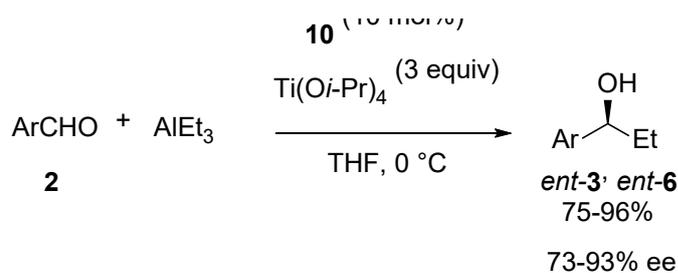


$R^1 = \text{Ph, } p\text{-Tol, } p\text{-F}$   
 $\text{}_3\text{CC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, 2\text{-Naph,}$   
 2-thienyl,  $p\text{-Tol, } o\text{-MeOC}_6\text{H}_4, 2\text{-Naph, Cy, PhCH=CH}$   
 $R^2 = n\text{-Bu, Me, } n\text{-Hex}$

**Scheme 6.** Alkylations of aromatic/aliphatic aldehydes with organolithium reagents in the presence of (*S*)-BINOL and phenyl-TADDOL ligands [19].

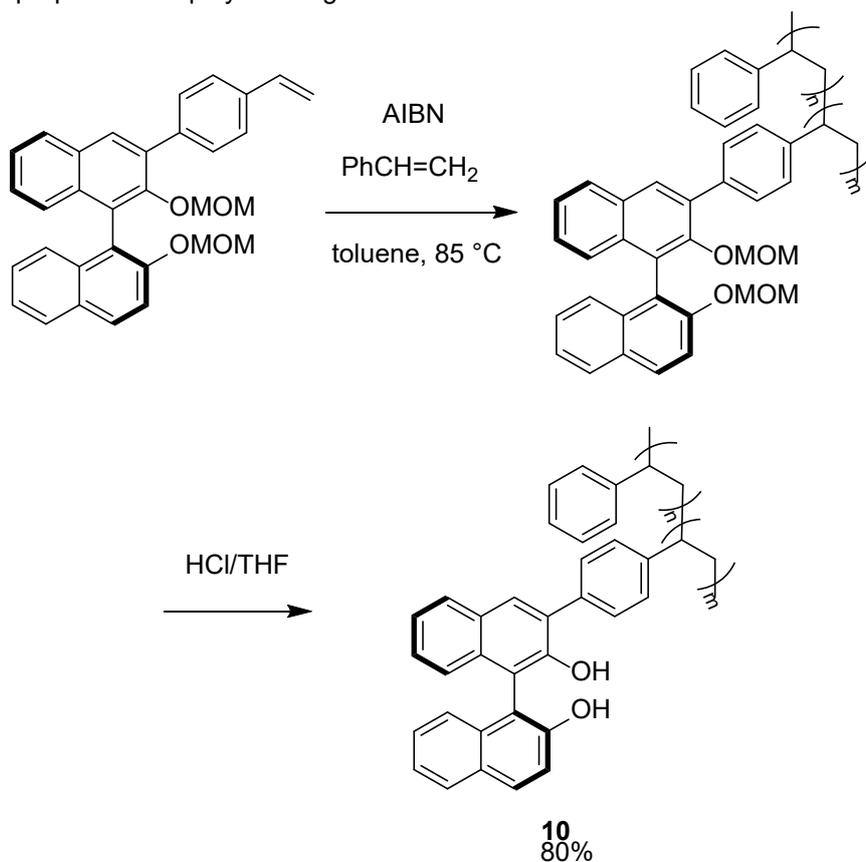
In addition, trialkylaluminum reagents are readily available and constitute valuable alkylating reagents for enantioselective additions to aldehydes **2**. Advantages of these reagents are low toxicities and high stabilities. In 2016, Yang et al. described the synthesis of novel polystyrene-supported (*S*)-BINOL-derived ligands via radical polymerization (Scheme

7) to be applied in the enantioselective titanium-catalyzed addition of triethylaluminum to aromatic aldehydes [20]. As depicted in Scheme 7, the process was performed at 0 °C in THF as solvent in the presence of 3 equivalents of  $\text{Ti}(\text{O}i\text{-Pr})_4$  and 10 mol% of heterogeneous optimal ligand **10**. Under these conditions, a series of chiral alcohols *ent-3* and *ent-6* were synthesized in both good to high yields (75-96%) and enantioselectivities (73-93% ee). The ligand could be easily recovered and reused up to four times.



Ar = Ph, *o*-MeOC<sub>6</sub>H<sub>4</sub>, *m*-MeOC<sub>6</sub>H<sub>4</sub>, *p*-ClC<sub>6</sub>H<sub>4</sub>, *p*-BrC<sub>6</sub>H<sub>4</sub>,  
*o*-PhC<sub>6</sub>H<sub>4</sub>, *m*-PhC<sub>6</sub>H<sub>4</sub>, *p*-PhC<sub>6</sub>H<sub>4</sub>, 1-Naph, 2-Naph, 9-anthryl

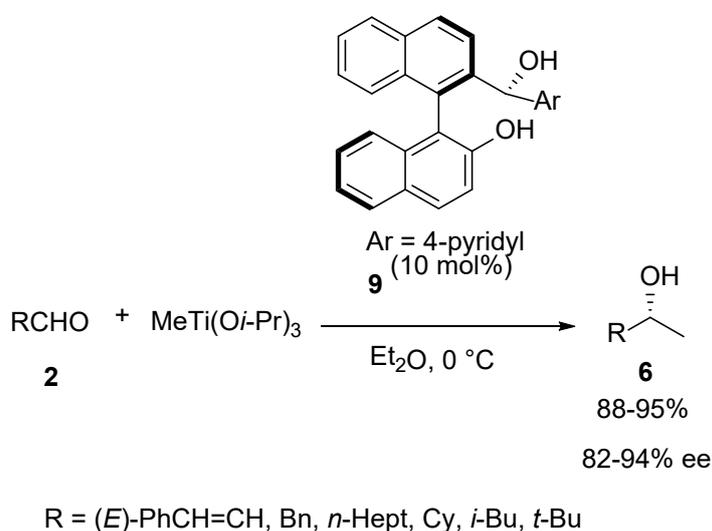
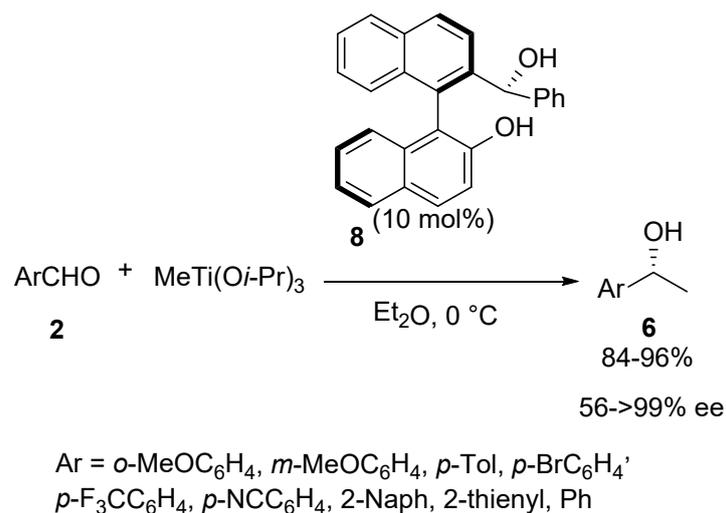
preparation of polymeric ligand **10**:



**Scheme 7.** Ethylation of aromatic aldehydes with AlEt<sub>3</sub> in the presence of (*S*)-BINOL-based polymeric ligand **10** [20].

In 1994, Seebach and Weber reported the first catalytic asymmetric addition of organotitanium reagents to aldehydes by using a TADDOL-derived chiral titanium catalyst [21]. In 2016, Macia and Fernandez-Ibanez reported a novel simple procedure to add

MeTi(*Oi*-Pr)<sub>3</sub> to aldehydes based on the use of Ar-BINMOL ligands **8** and **9** [22]. It presented several advantages in comparison with the TADDOL-based methodologies, such as higher reaction temperatures, shorter reaction times and no requirement of using Ti(*Oi*-Pr)<sub>4</sub>. As illustrated in Scheme 8, the methylation of aromatic aldehydes **2** performed at 0 °C in diethyl ether as solvent in the presence of 10 mol% of ligand **8** led to the formation of the corresponding chiral methyl carbinols **6** in uniformly high yields (84-96%) and moderate to excellent enantioselectivities (56->99% ee). Actually, the enantioselectivities were ≥87% ee for various (hetero)aromatic aldehydes excepted for sterically hindered *o*-methoxybenzaldehyde which provided the corresponding alcohol with only 56% ee. The authors found that the use of closely related ligand **9** under similar conditions allowed aliphatic aldehydes **2** to react with MeTi(*Oi*-Pr)<sub>3</sub> to give the corresponding chiral products **6** in both high yields (88-95%) and enantioselectivities (82-94% ee), as shown in Scheme 8.



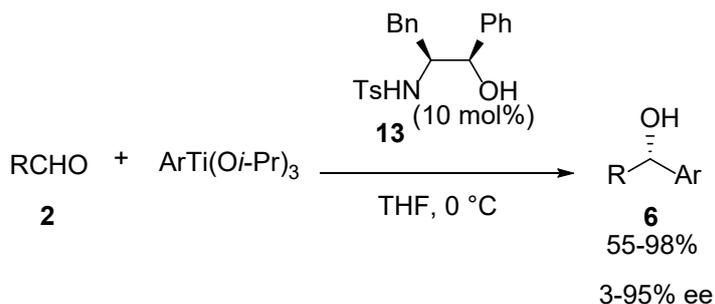
**Scheme 8.** Methylations of aromatic/aliphatic aldehydes with MeTi(O*i*-Pr)<sub>3</sub> in the presence of Ar-BINMOL ligands **8** and **9** [22].

The high reactivity of common organometallic reagents is often not compatible with the use of functionalized substrates. In this context, owing to their lower reactivity, organozirconium reagents bearing functionalities have been recently employed as nucleophiles toward carbonyl compounds. Therefore in 2018, Macia and Fernandez-Ibanez reported the first enantioselective titanium-catalyzed addition of alkylzirconium species to aromatic aldehydes **2** which was performed in the presence of 20 mol% of chiral Ph-BINMOL ligand **8** [23].



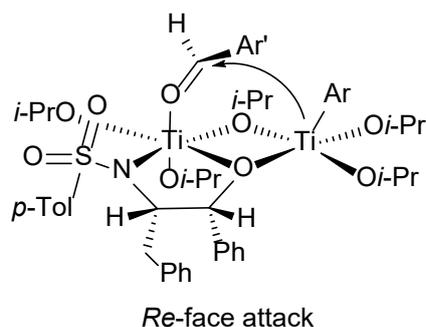
## 2.2. Arylation of aldehydes and ketones

In 1994, Seebach and Weber described the first asymmetric catalytic addition of  $\text{PhTi}(\text{O}i\text{-Pr})_3$  to aldehydes promoted by a TADDOL-derived titanium catalyst, which provided enantioselectivities of up to 99% ee [21]. However, this process presented the disadvantage to require a low temperature ( $-78\text{ }^\circ\text{C}$ ). Later in 2010s, Gau and Zhou demonstrated the possibility to perform (hetero)arylations of aldehydes at  $0\text{ }^\circ\text{C}$  [25]. Ever since, other highly efficient chiral ligands have been applied to promote the asymmetric titanium-catalyzed aryl transfer to aldehydes at  $0\text{ }^\circ\text{C}$ . For example, these authors investigated chiral *N*-sulfonylated amino alcohol ligands in the addition of  $\text{ArTi}(\text{O}i\text{-Pr})_3$  to aldehydes **2**, in 2015 [26]. As shown in Scheme 10, the process performed at  $0\text{ }^\circ\text{C}$  in the presence of 10 mol% of optimal ligand **13** in THF as solvent afforded the corresponding chiral alcohols **6** in good to quantitative yields (55-98%) and low to excellent enantioselectivities (3-95% ee). The best results (83-98% yields, 72-95% ee) were achieved in the asymmetric addition of  $\text{PhTi}(\text{O}i\text{-Pr})_3$  to aromatic aldehydes while the same addition to aliphatic aldehydes provided lower enantioselectivities (56-84% ee) albeit combined with high yields (85-96%). Other aryltitanium compounds ( $\text{Ar} \neq \text{Ph}$ ) reacted with benzaldehyde with generally moderate to high enantioselectivities (53-90% ee) but lower enantioselectivities (3-52% ee) were obtained for sterically hindered aryltitanium compounds, such as *ortho*-substituted aromatic substrates. On the basis of mechanistic studies, the authors proposed the transition state depicted in Scheme 10 in which the phenyl group of the aryl aldehyde pointed toward the same side of the bridging oxygen donor of the chiral ligand. This resulted in a *Re*-face attack of the nucleophile to the aldehyde.



R = *o*-MeOC<sub>6</sub>H<sub>4</sub>, *m*-MeOC<sub>6</sub>H<sub>4</sub>, *p*-MeOC<sub>6</sub>H<sub>4</sub>, *o*-Tol, *m*-Tol, *p*-Tol, *o*-ClC<sub>6</sub>H<sub>4</sub>, *m*-ClC<sub>6</sub>H<sub>4</sub>, *p*-ClC<sub>6</sub>H<sub>4</sub>, *o*-BrC<sub>6</sub>H<sub>4</sub>, *m*-BrC<sub>6</sub>H<sub>4</sub>, *p*-BrC<sub>6</sub>H<sub>4</sub>, *o*-FC<sub>6</sub>H<sub>4</sub>, *p*-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>, *o*-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, *m*-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, *p*-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, 1-Naph, 2-Naph, 2-furyl, (*E*)-PhCH=CH, *i*-Bu, *t*-Bu, Cy, Ph  
 Ar = Ph, *p*-MeOC<sub>6</sub>H<sub>4</sub>, *p*-Tol, *p*-ClC<sub>6</sub>H<sub>4</sub>, *p*-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>, 2-Naph, 1-Naph, *o*-MeOC<sub>6</sub>H<sub>4</sub>, *o*-ClC<sub>6</sub>H<sub>4</sub>, *p*-ClC<sub>6</sub>H<sub>4</sub>, *p*-Tol

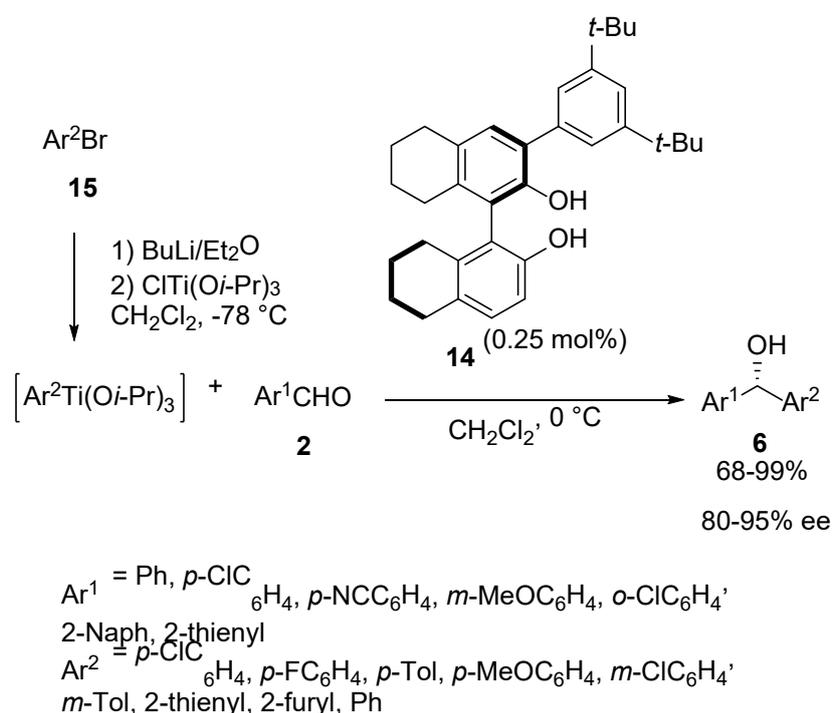
proposed transition state for aryl aldehydes Ar'CHO:



**Scheme 10.** Arylation of aromatic/aliphatic aldehydes with ArTi(Oi-Pr)<sub>3</sub> in the presence of chiral *N*-sulfonylated 1,2-amino alcohol ligand **13** [26].

In most enantioselective arylations of aromatic aldehydes, more than 5 mol% of catalyst loadings are employed, limiting scale-up applications. In 2016, Harada et al. demonstrated that the activity of chiral titanium catalysts derived from H<sub>8</sub>-BINOL ligands was enhanced by the presence of a sterically hindered substituent at the 3-position in the asymmetric arylation of aromatic aldehydes with Ar<sup>2</sup>Ti(Oi-Pr)<sub>3</sub> [27]. As illustrated in Scheme 11, only 0.25 mol% of catalyst loading in 3-substituted (*R*)-H<sub>8</sub>-BINOL ligand **14** was sufficient to promote the

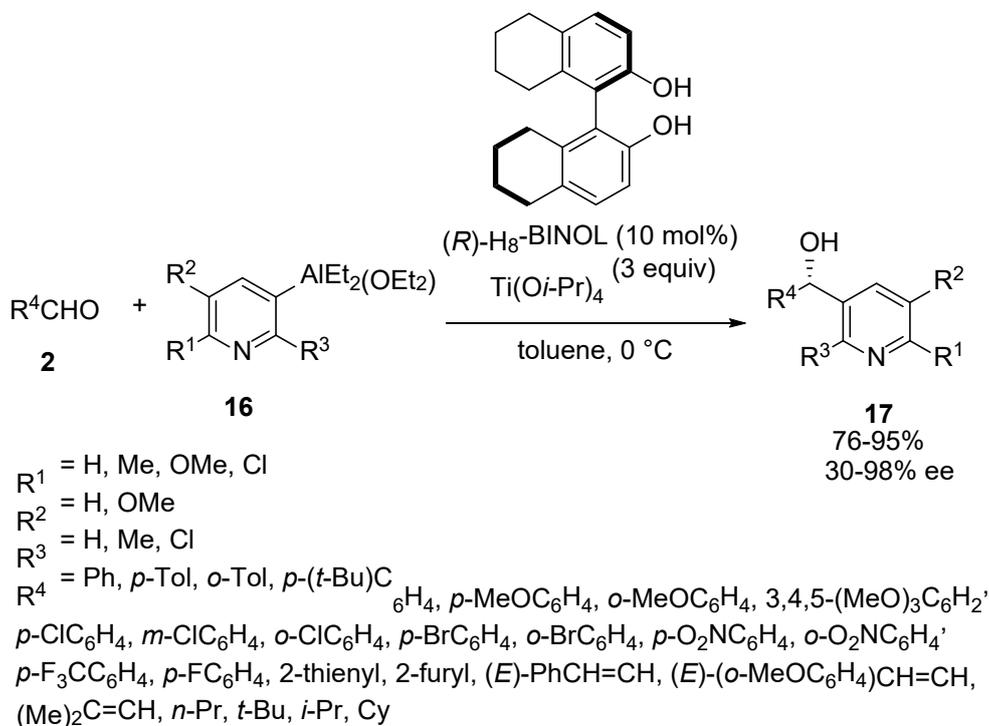
addition of  $\text{Ar}^2\text{Ti}(\text{O}i\text{-Pr})_3$  to various aromatic aldehydes **2** performed at 0 °C in dichloromethane as the solvent. The corresponding chiral alcohols **6** were obtained in good to high yields (68-99%) and uniformly high enantioselectivities (80-95% ee). The (hetero)aryltitanium reagents were in situ generated from the corresponding bromides **15**, as shown in Scheme 11.



**Scheme 11.** Arylation of aromatic aldehydes with  $\text{Ar}^2\text{Ti}(\text{O}i\text{-Pr})_3$  in the presence of 3-substituted (*R*)- $\text{H}_8$ -BINOL ligand **14** [27].

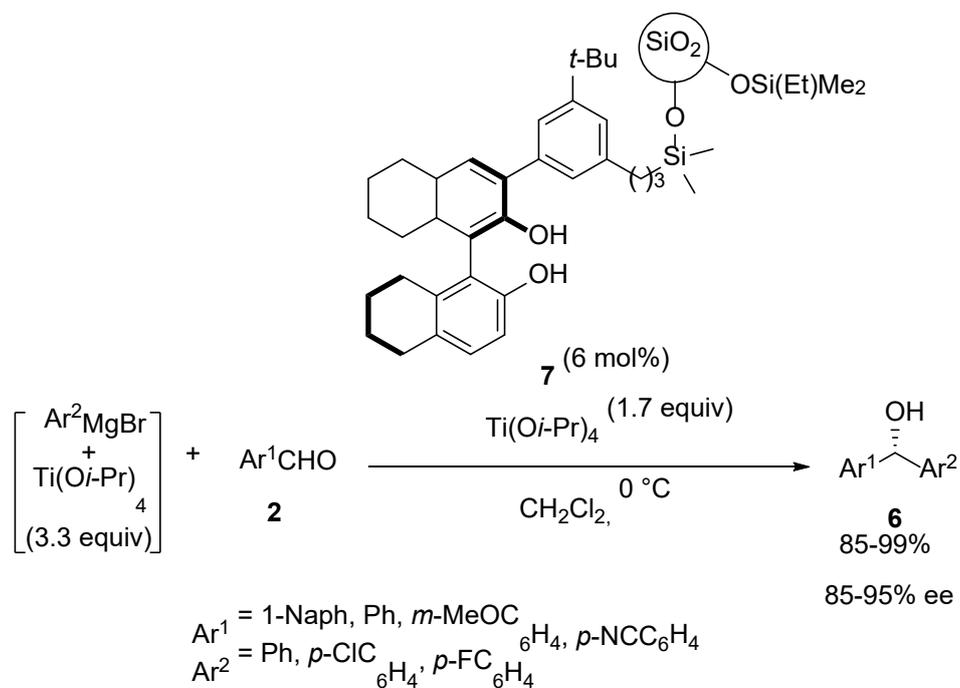
Many chiral diaromatic alcohols exhibiting heteroaryl moieties, such as pyridyl, are biologically active [28]. With the aim of finding a direct route to these important products for medicinal chemistry, Zhou and Zhang developed in 2015 the first asymmetric addition of pyridyl nucleophiles to aldehydes [29]. The process involved pyridyl aluminum reagents **16**

as nucleophiles which were condensed at 0 °C to a range of aldehydes **2** in toluene as solvent. Performed in the presence of 10 mol% of (*R*)-H<sub>8</sub>-BINOL as ligand and 3 equivalents of Ti(*Oi*-Pr)<sub>4</sub>, the heteroarylation led to the corresponding chiral 3-pyridyl methanols **17** in uniformly high yields (76-95%) and low to excellent enantioselectivities (30-98% ee), as illustrated in Scheme 12. The highest enantioselectivities of up to 98% ee were generally obtained in the reaction of aromatic aldehydes with non-substituted 3-pyridyl aluminum reagent **16a** (R<sup>1</sup> = R<sup>2</sup> = R<sup>3</sup> = H) while substituted 3-pyridyl aluminum reagents bearing an electron-donating group on the pyridyl ring afforded the corresponding diarylalcohols in generally lower enantioselectivities (30-85% ee). Moreover, the catalyst system was compatible with aliphatic aldehydes, since their reaction with 3-pyridyl aluminum reagent **16a** led to the corresponding alcohols in high yields (85-95%) and moderate to high enantioselectivities (49-81% ee).



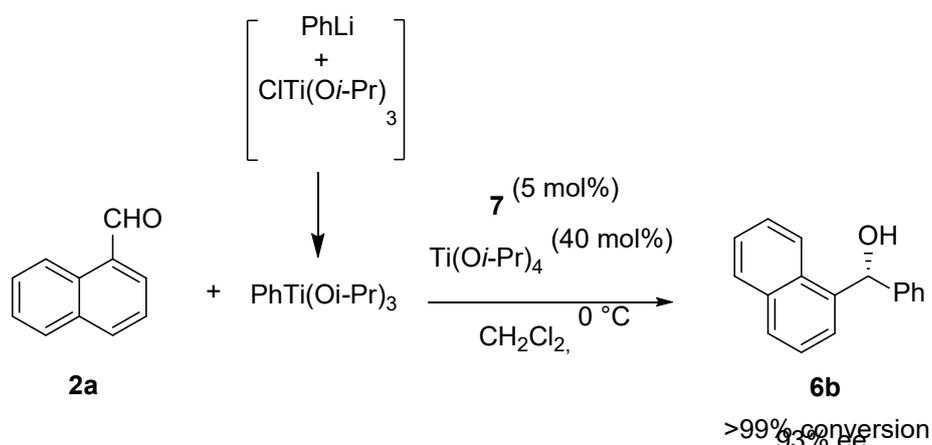
**Scheme 12.** Heteroarylation of aromatic/aliphatic aldehydes with pyridyl aluminum reagents in the presence of (*R*)-H<sub>8</sub>-BINOL [29].

In 2017, recyclable silica-supported H<sub>8</sub>-BINOL-derived ligand **7** was applied at 6 mol% of catalyst loading by Harada et al. to promote the arylation of aromatic aldehydes **2** with aromatic Grignard reagents in dichloromethane as solvent [14]. The reaction was performed at 0 °C in the presence of 1.7 equivalent of Ti(O*i*-Pr)<sub>4</sub>, leading to the corresponding chiral diaryl alcohols **6** in both homogeneous high yields (85-99%) and enantioselectivities (85-95% ee), as illustrated in Scheme 13. The process involved the addition of a mixture of the Grignard reagent with 3.3 equivalents of Ti(O*i*-Pr)<sub>4</sub> to a CH<sub>2</sub>Cl<sub>2</sub> solution of the aldehyde with 1.7 equivalents of Ti(O*i*-Pr)<sub>4</sub> and the chiral ligand at 0 °C. The heterogeneous catalyst could be reused for up to ten cycles. Later in 2018, the same authors demonstrated that these reactions could be performed under continuous-flow conditions with comparable yields (40-99%) and enantioselectivities (81-96% ee) [30].



**Scheme 13.** Arylation of aromatic aldehydes with aryl Grignard reagents in the presence of silica-supported H<sub>8</sub>-BINOL-derived ligand **7** [14].

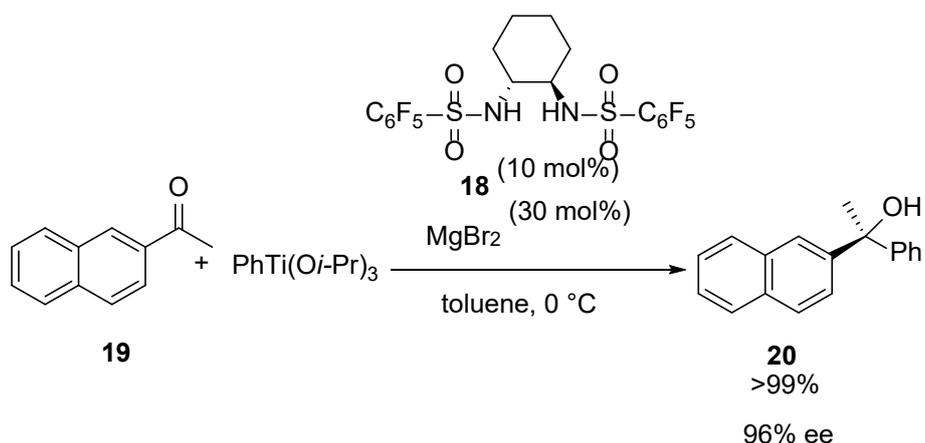
The same immobilized catalyst was found applicable to promote the enantioselective addition of PhTi(O*i*-Pr)<sub>3</sub>, in situ generated from PhLi and ClTi(O*i*-Pr)<sub>3</sub>, to 1-naphthaldehyde **2a** [30]. In this case, only 5 mol% of ligand **7** in combination with 40 mol% of Ti(O*i*-Pr)<sub>4</sub> were sufficient to catalyze the addition, affording the corresponding alcohol **6b** in 93% ee with complete conversion (Scheme 14). The recycled ligand could be reused up to ten times without losing enantioselectivity.



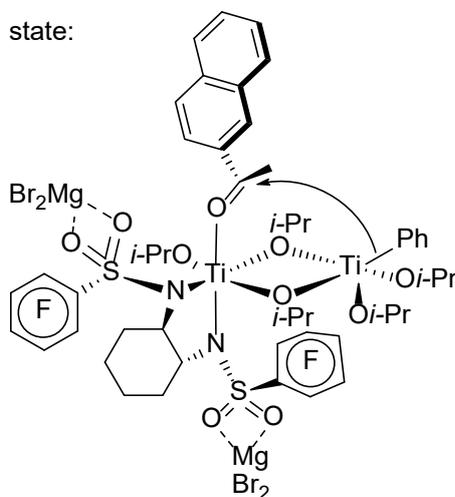
**Scheme 14.** Phenylation of naphthaldehyde with phenyl lithium in the presence of silica-supported H<sub>8</sub>-BINOL-derived ligand **7** [30].

In comparison with aldehydes, the catalytic asymmetric addition of alkyl/aryl reagents to ketones is more challenging because of their lower electrophilicity. However, this methodology represents the most direct route to prepare chiral tertiary alcohols which are

versatile building blocks for the synthesis of many drugs and natural products [31]. In the past two decades, chiral zinc and titanium catalysts have been the two principal systems to promote these reactions. In an example reported in 2015, Gau and Zhou employed a titanium complex derived from chiral *N,N'*-sulfonylated cyclohexane-1,2-diamine ligand **18** to catalyze the asymmetric phenylation of 2'-acetonaphthone **19** with  $\text{PhTi}(\text{O}i\text{-Pr})_3$  [32]. As presented in Scheme 15, the reaction was performed at 0 °C in toluene as solvent in the presence of 10 mol% of this chiral ligand and 30 mol% of  $\text{MgBr}_2$  as an additive. It provided the corresponding almost enantiopure tertiary alcohol **20** (96% ee) in quantitative yield (>99%). The authors proposed the transition state depicted in Scheme 15 in which both the two sulfonyl groups coordinated to two equivalents of  $\text{MgBr}_2$ , forming a pocket of suitable size allowing the insertion of the planar aromatic ring of 2'-acetonaphthone **19** to be added by the phenyl nucleophile.



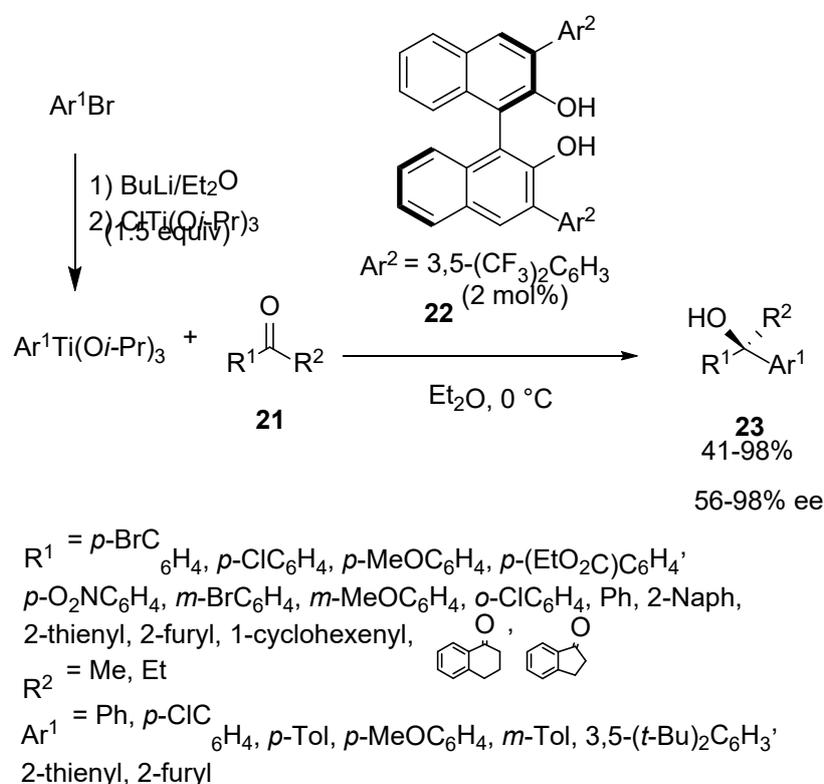
proposed transition state:



**Scheme 15.** Phenylation of 2'-acetonaphthone with  $\text{PhTi(Oi-Pr)}_3$  in the presence of *N,N'*-sulfonylated cyclohexane-1,2-diamine ligand **18** [32].

In 2017, Harada et al. developed a general methodology for asymmetric (hetero)arylation of ketones with  $\text{Ar}^1\text{Ti(Oi-Pr)}_3$  [33]. This organotitanium reagent was in situ generated from the corresponding bromide through lithiation with *n*-BuLi followed by transmetalation of the resulting organolithium species with  $\text{ClTi(Oi-Pr)}_3$ . Then,  $\text{Ar}^1\text{Ti(Oi-Pr)}_3$  was added at 0 °C to ketones **21** in  $\text{Et}_2\text{O}$  as the solvent in the presence of only 2 mol% of (*R*)-BINOL-derived ligand **22** to afford the corresponding chiral tertiary alcohols **23** in moderate to excellent yields (41-93%) and enantioselectivities (56-94% ee), as depicted in Scheme 16. Moreover, heteroaryl titanium reagents ( $\text{Ar}^1 = 2\text{-thienyl, 2-furyl}$ ) also reacted smoothly to give the

corresponding products in even higher yields (80-98%) and enantioselectivities (87-98% ee) than aryl titanium reagents. In addition to acyclic aromatic and heteroaromatic methyl ketones, cyclic aromatic ketones such as indanones were compatible and provided excellent enantioselectivities (80-87% ee). Moreover, a dialkyl ketone ( $R^1 = 1\text{-cyclohexenyl}$ ,  $R^2 = \text{Me}$ ) also reacted smoothly to produce the corresponding alcohol in 70% yield and 94% ee. The lowest enantioselectivity (56% ee) was obtained in the reaction of phenyl ethyl ketone ( $R^1 = \text{Ph}$ ,  $R^2 = \text{Et}$ ) with *p*-chlorophenyltitanium reagent ( $\text{Ar}^1 = p\text{-ClC}_6\text{H}_4$ ).

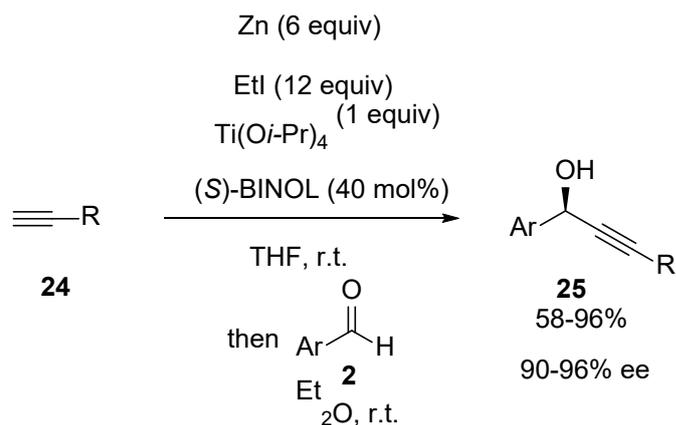


**Scheme 16.** (Hetero)arylation of ketones with  $\text{Ar}^1\text{Ti}(\text{O}i\text{-Pr})_3$  in the presence of (*R*)-BINOL-derived ligand **22** [33].

### 2.3. Alkynylations of aldehydes and ketones

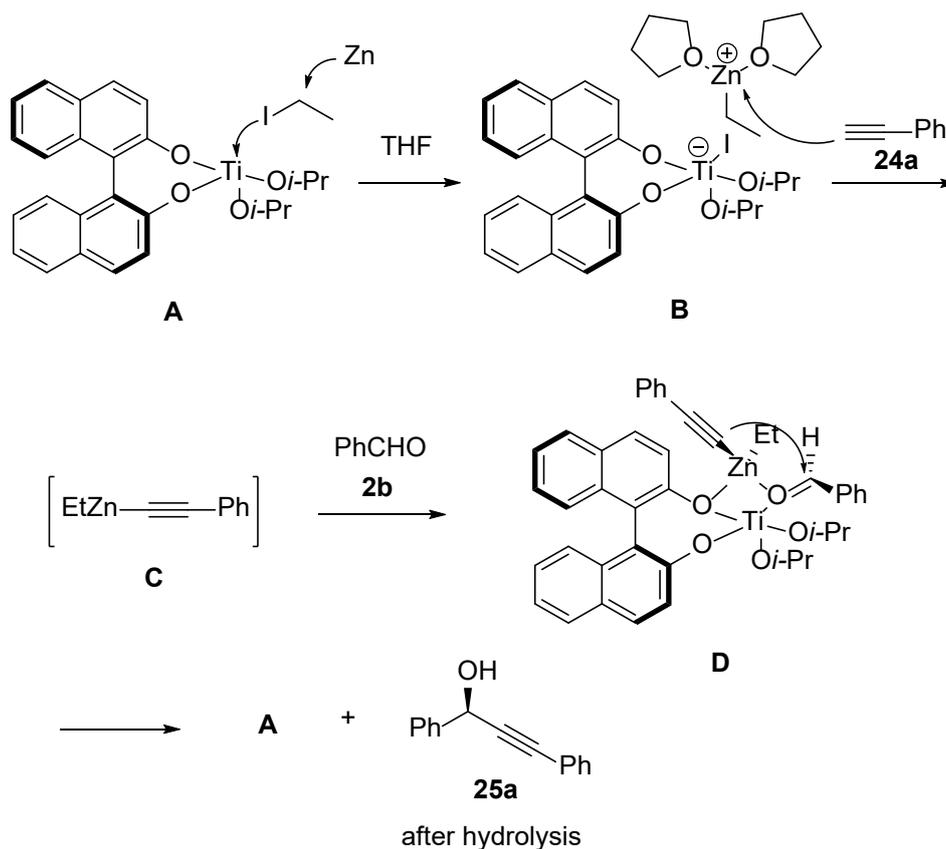
The enantioselective addition of organometallic alkynyl derivatives to carbonyl compounds is the most direct route to chiral propargylic alcohols which constitute key building blocks for the synthesis of a range of important chiral molecules [34]. The first examples of enantioselective titanium-catalyzed alkylation of aldehydes were independently reported by Chan and Pu, in 2002 [35]. The catalyst system was a combination of BINOL as ligand,  $\text{ZnEt}_2$  and  $\text{Ti}(\text{O}i\text{-Pr})_4$ . The alkyne reacted by heating with  $\text{ZnEt}_2$  to give the corresponding alkynylzinc intermediate which further added to the aldehyde in the presence of  $\text{Ti}(\text{O}i\text{-Pr})_4$  and chiral BINOL ligand to give the final propargylic alcohol in high enantioselectivity of up to 98% ee. In order to avoid the use of combustible  $\text{ZnEt}_2$  employed in all the procedures developed so far, Pu and Yu discovered in 2015 that Zn could react with EtI activated at room temperature by a BINOL/ $\text{Ti}(\text{O}i\text{-Pr})_4$  catalyst system in THF as solvent [36]. As shown in Scheme 17, a Lewis acid complex **A** generated from  $\text{Ti}(\text{O}i\text{-Pr})_4$  and (*S*)-BINOL promoted the oxidative addition of Zn to EtI to give ionic intermediate **B**. In the latter, THF molecules coordinated to the electron-deficient Zn(II) center to stabilize the cationic zinc alkyl unit. Coordination of the triple bond of phenylacetylene **24a** ( $\text{R} = \text{Ph}$ ) to the electron-deficient zinc center of intermediate **B** could activate the deprotonation of the terminal alkyne to generate the nucleophilic alkynylzinc reagent **C**. Its further combination with complex **A** and benzaldehyde **2b** ( $\text{Ar} = \text{Ph}$ ) could provide intermediate **D**. Migration of the alkynyl group from Zn to the coordinated carbonyl group of the aldehyde afforded a chiral zinc propargylate intermediate which further regenerated chiral complex **A** and led to final propargylic alcohol **25a** ( $\text{Ar} = \text{R} = \text{Ph}$ ) after hydrolysis. This methodology was performed at room temperature in THF as the solvent in the presence of 6 equivalents of Zn, 12 equivalents of EtI, 1 equivalent of  $\text{Ti}(\text{O}i\text{-Pr})_4$  and 40 mol% of (*S*)-BINOL as the ligand. To this mixture including alkyne **24** was further added aldehyde **2** in solution in  $\text{Et}_2\text{O}$  as less nucleophilic solvent than THF. As illustrated in Scheme 17, a range of aromatic aldehydes **2** exhibiting electron-withdrawing as

well as electron-donating substituents on the phenyl ring in *ortho*-, *meta*- or *para*-position reacted smoothly with phenylacetylene and also various aliphatic alkynes to give the corresponding chiral propargylic alcohols **25** in good to quantitative yields (58-96%) and uniformly excellent enantioselectivities (90-96% ee). Even an heteroaromatic (Ar = 2-furyl) aldehyde reacted with a high enantioselectivity (91% ee) albeit combined with a moderate yield (60%). In most cases, phenylacetylene **24a** gave higher yields than aliphatic alkynes (75-96% vs 58-80%).



R = Ph, 1-cyclohexenyl, BnCH<sub>2</sub>, *n*-Hex, *n*-Bu  
 Ar = Ph, *p*-Tol, *m*-Tol, *o*-Tol, *p*-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>, *p*-FC<sub>6</sub>H<sub>4</sub>, *p*-ClC<sub>6</sub>H<sub>4</sub>, *p*-BrC<sub>6</sub>H<sub>4</sub>,  
*p*-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, *p*-MeOC<sub>6</sub>H<sub>4</sub>, *m*-ClC<sub>6</sub>H<sub>4</sub>, 1-Naph, 2-Naph, 2-furyl

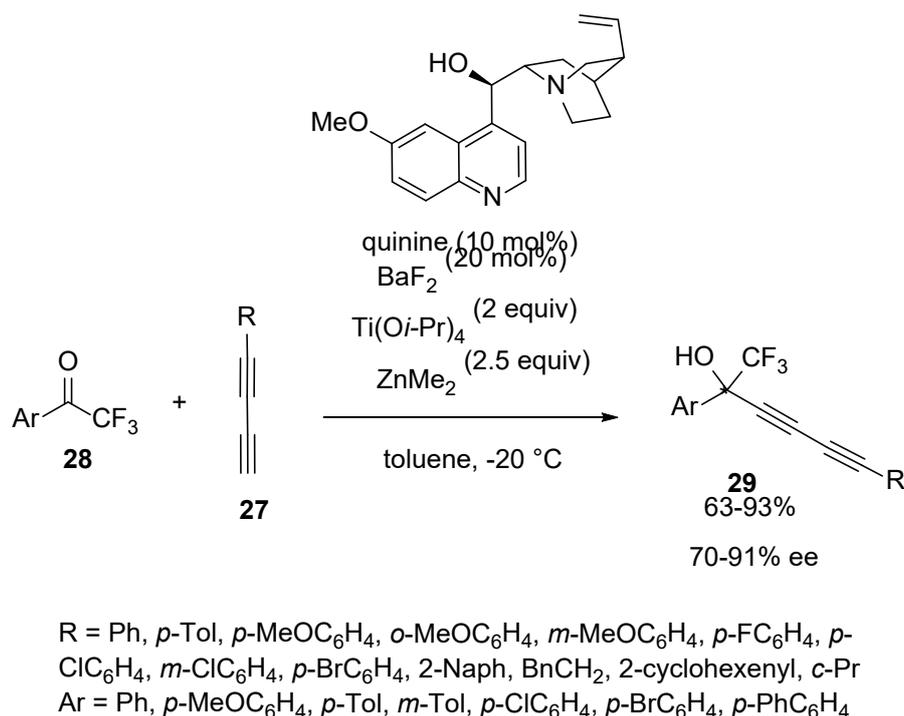
proposed mechanism (with Ar = R = Ph):



**Scheme 17.** Alkylation of aromatic aldehydes with terminal alkynes in the presence of (S)-BINOL [36].



On the other hand, the alkynylation of ketones is less developed than that of aldehydes because of the lower reactivity of ketones. The first reactions were described by the group of Tan in 1999 and later by that of Jiang in 2002 [42]. This is only in 2004 that chiral titanium catalysts derived from BINOL were applied by Cozzi and Alesi to promote these nucleophilic additions [43]. Chiral hydroxysulfonamide ligands also provided good results with methyl ketones [44]. Among ketones, trifluoromethyl ketones are challenging substrates for the asymmetric titanium-promoted alkynylation because of the presence of the strongly electron-withdrawing fluorine atoms. Indeed, these activating trifluoromethyl group renders the ketone highly reactive. In 2011, Ma et al. described the first efficient asymmetric addition of alkynes to trifluoromethyl ketones which provided enantioselectivities of up to 94% ee in the presence of cinchona alkaloid ligands [45]. Moreover, the use of 1,3-diynes is more challenging than that of simple alkynes since it provides chiral diynols, as already described by Pu et al. in asymmetric additions to aldehydes, in 2011 [46]. In 2016, Ma et al. investigated the addition of this type of nucleophiles to aromatic trifluoromethyl ketones (Scheme 19) [47]. Performed in the presence of a combination of 2.5 equivalents of  $ZnMe_2$ , 2 equivalents of  $Ti(Oi-Pr)_4$ , 20 mol% of  $BaF_2$  as an additive and 10 mol% of quinine as chiral ligand, the enantioselective addition of terminal 1,3-diynes **27** to a range of trifluoromethyl ketones **28** afforded the corresponding chiral trifluoromethylated diynols **29** in both good to high yields (63-93%) and enantioselectivities (70-91% ee). The catalyst system was compatible with variously substituted aromatic trifluoromethyl ketones and aromatic as well as aliphatic 1,3-diynes. This simple methodology represented a novel synthetic route to the frameworks of many biologically active products, such as an analogue of the anti-HIV Efavirenz synthesized from 1-cyclopropyl-1,3-diyne (R = Cy) and 5-chloro-2-nitro-phenyl trifluoromethyl ketone (Ar = 5-Cl-2-O<sub>2</sub>N-C<sub>6</sub>H<sub>3</sub>).

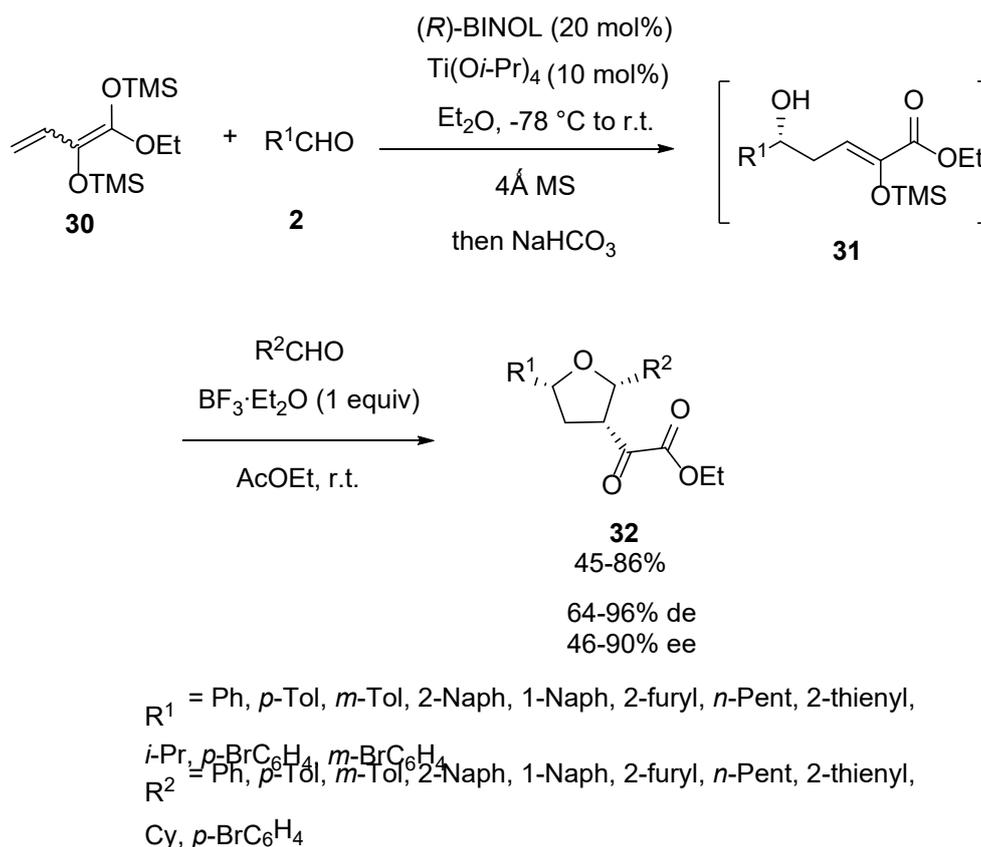


**Scheme 19.** Alkynylation of aromatic trifluoromethyl ketones with 1,3-diynes in the presence of quinine [47].

#### 2.4. Allylations and vinylations of aldehydes

The titanium-catalyzed addition of allylic nucleophiles to carbonyl compounds led to the corresponding homoallylic alcohols which constitute important building blocks in organic synthesis [48]. While the first allylation was reported by Hosomi and Sakurai in 1976, using TiCl<sub>4</sub> as achiral promotor [49], the first asymmetric version was reported in 1982 by Hayashi and Kumada based on the use of a chiral allyltitanium reagent [50]. It is only in 1993 that Umani-Ronchi [51] and Keck [52] independently reported the first enantioselective titanium-catalyzed allylation of aldehydes using a BINOL titanium catalyst and allyl stannanes as allylation reagents. Ever since, a variety of BINOL-derived ligands have been developed by several groups to be used in these enantioselective titanium-catalyzed reactions mostly based

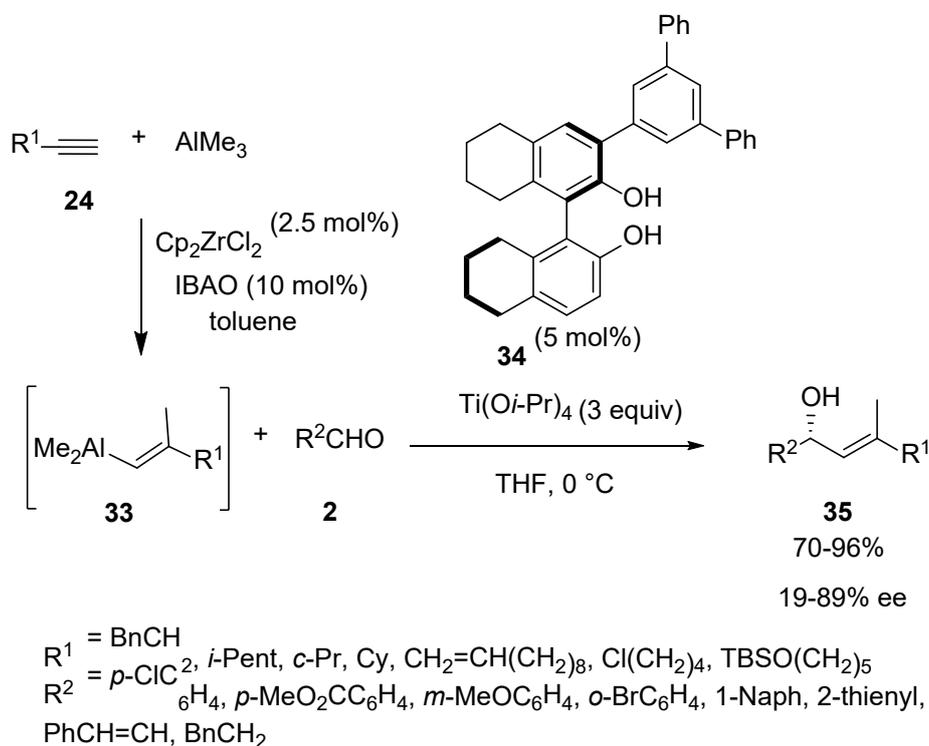
on the use of allyltributyltin as allylation reagent [53]. In 2019, Schneider and Hoffmeyer described a one-pot asymmetric synthesis of 2,3,5-trisubstituted tetrahydrofurans initiated by an enantioselective titanium-catalyzed vinylogous Mukaiyama aldol reaction of bis(silyl) dienediolate **30** with aldehydes **2** [54]. This first step was promoted by a chiral titanium catalyst in situ generated from only 10 mol% of  $\text{Ti}(\text{O}i\text{-Pr})_4$  and 20 mol% of (*R*)-BINOL. Performed at -78 °C to room temperature in  $\text{Et}_2\text{O}$  as the solvent, the reaction delivered the corresponding chiral intermediate allylic alcohols **31** which were directly submitted to  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ -mediated Prins-type cyclization with a second equivalent of aldehyde **2**, leading to chiral 2,3,5-trisubstituted tetrahydrofurans **32** exhibiting three stereogenic centers (Scheme 20). These products were obtained in moderate to high yields (45-86%), diastereo- (64-96% de) and enantioselectivities (46-90% ee). The reaction conditions were compatible with (hetero)aromatic and aliphatic aldehydes but generally the latter substrates provided poorer results. This simple one-pot methodology represented a rapid access to chiral substituted tetrahydrofurans which constitute the frameworks of many natural and bioactive products.



**Scheme 20.** Alkylation of aldehydes with a bis(silyl) dienediolate in the presence of (*R*)-BINOL and one-pot synthesis of 2,3,5-trisubstituted tetrahydrofurans [54].

Highly efficient chiral catalysts for the asymmetric vinylation of aldehydes have been developed by different groups [55]. A novel methodology was described by Harada and Morimoto, in 2015 [56]. It involved trisubstituted (*E*)-vinylaluminum reagents **33** regio- and stereoselectively in situ generated through zirconium-catalyzed carboalumination of the corresponding alkynes **24** with  $\text{AlMe}_3$ . As shown in Scheme 21, these intermediates were performed in toluene in the presence of 10 mol% of isobutylaluminumoxane (IBAO) as cocatalyst and 2.5 mol% of  $\text{Cp}_2\text{ZrCl}_2$  as catalyst. The latter were subsequently added at 0 °C to a THF solution of aldehyde **2**, 3 equivalents of  $\text{Ti(Oi-Pr)}_4$  and only 5 mol% of (*R*)-H<sub>8</sub>-BINOL-derived ligand **34**. The process afforded the corresponding chiral  $\beta,\beta$ -disubstituted allylic alcohols **35** in high yields (70-96%) and low to high enantioselectivities (19-89% ee).

A range of aromatic, heteroaromatic as well as aliphatic aldehydes provided good to high enantioselectivities (66-89% ee) while the reaction of *o*-bromobenzaldehyde provided the lowest enantioselectivity (19% ee). A variety of alkynes were tolerated, including those bearing an olefinic moiety, a cycloalkyl group, a chlorine atom, or a silyloxy group. This novel methodology offered a rapid one-step asymmetric synthesis of trisubstituted allylic alcohols from readily available aldehydes and terminal alkynes.



**Scheme 21.** Vinylation of aldehydes with in situ generated trisubstituted (*E*)-vinylaluminum reagents in the presence of (*R*)-H<sub>8</sub>-BINOL-derived ligand **34** [56].

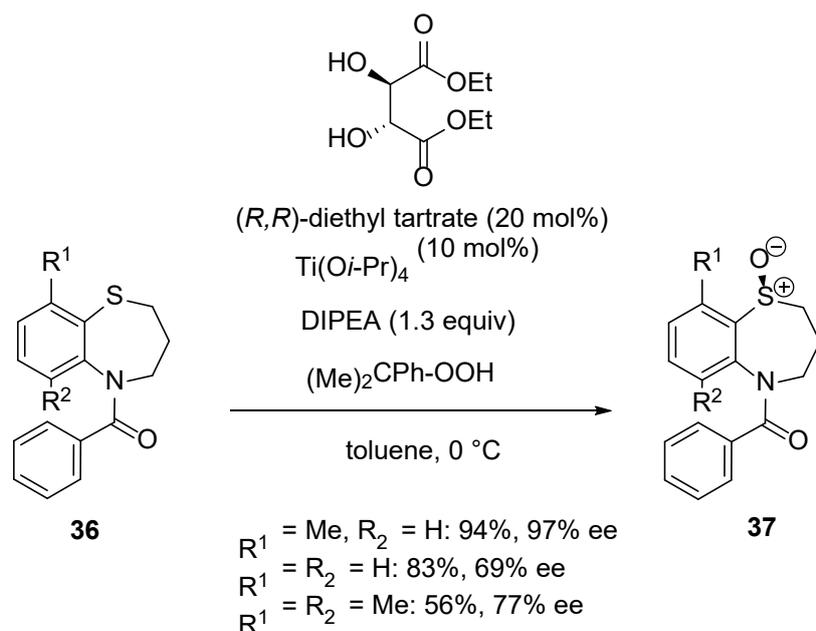
### 3. Enantioselective titanium-catalyzed sulfoxidations

Chiral sulfoxides constitute ones of the most important sulfur compounds [57] related to their extensive use in asymmetric synthesis as either chiral auxiliaries or ligands [58].

Furthermore, they constitute the frameworks of a wide range of natural and bioactive products. Consequently, their synthesis is challenging [59] with the most direct methodology based on the asymmetric oxidation of nonsymmetric sulfides [60]. Among metal catalysts employed to promote these processes, titanium complexes have been the most efficient [61].

### 3.1. With alkyl hydroperoxides as oxidants

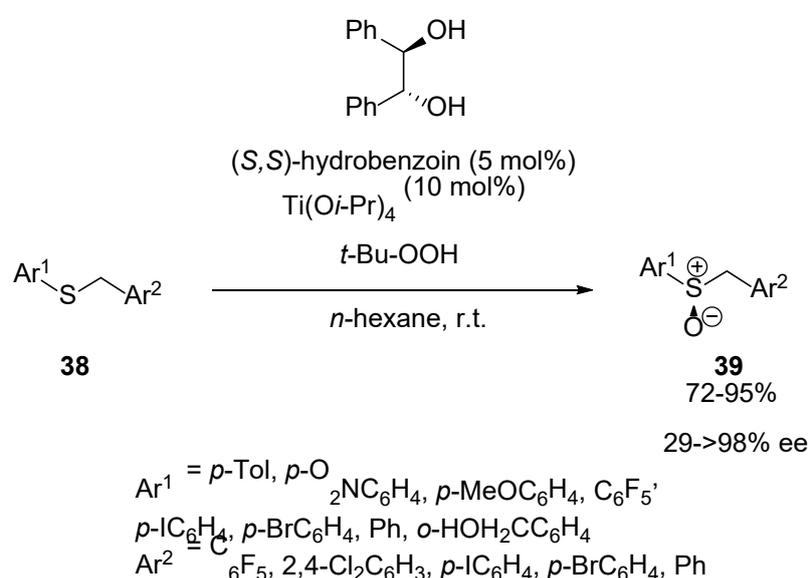
In 1984, Kagan [61a-b] and Modena [61c] demonstrated that the combination of  $\text{Ti}(\text{O}i\text{-Pr})_4$  with chiral diethyltartrate could enantioselectively promote the oxidation of sulfides in the presence of alkyl hydroperoxides as oxidants. Ever since, many variants of this methodology have been developed. For example, Takahashi et al. described in 2017 the first asymmetric oxidation of *N*-benzoyl-1,5-benzothiazepines **36** with cumene hydroperoxide in the presence of a catalytic amount of a chiral titanium catalyst derived from tartrates [62]. As presented in Scheme 22, the process was performed at 0 °C in toluene as the solvent in the presence of only 10 mol% of  $\text{Ti}(\text{O}i\text{-Pr})_4$  and 20 mol% of (*R,R*)-diethyl tartrate. The reaction of *N*-benzoyl-1,5-benzothiazepines **36** with cumene hydroperoxide in the presence of 1.3 equivalent of DIPEA as base led to the corresponding (*S*)-sulfoxides **37** in both good to high yields (56-94%) and enantioselectivities (69-97% ee).



**Scheme 22.** Oxidation of *N*-benzoyl-1,5-benzothiazepines in the presence of (*R,R*)-diethyl tartrate [62].

Along with tartrates, other chiral 1,2-diols have also been successfully applied as ligands in this type of reactions [63]. For example in 2006, Cardellicchio described the use of chiral hydrobenzoin as ligand in asymmetric titanium-catalyzed sulfoxidations with *tert*-butyl hydroperoxide [64]. This methodology was generalized in 2015 to a wide range of aryl benzyl sulfides bearing coordinating moieties on their phenyl rings [65]. Therefore, the oxidation of sulfides **38** with *tert*-butyl hydroperoxide performed at room temperature in hexane as the solvent in the presence of only 5 mol% of  $\text{Ti}(\text{O}i\text{-Pr})_4$  and the same quantity of (*S,S*)-hydrobenzoin as ligand led to the formation of the corresponding (*R*)-sulfoxides **39** in good to high yields (72-95%) and low to excellent enantioselectivities (29->98% ee), as illustrated in Scheme 23. Especially, the oxidations of 2,3,4,5,6-pentafluorobenzyl sulfides exhibiting nitro-, methyl- or methoxy-substituents in the *para*-position of the phenyl ring ( $\text{Ar}^1 = p\text{-NO}_2\text{C}_6\text{H}_4$ , *p*-Tol, *p*-MeOC<sub>6</sub>H<sub>4</sub>) were performed completely enantioselectively (>98% ee) with good to

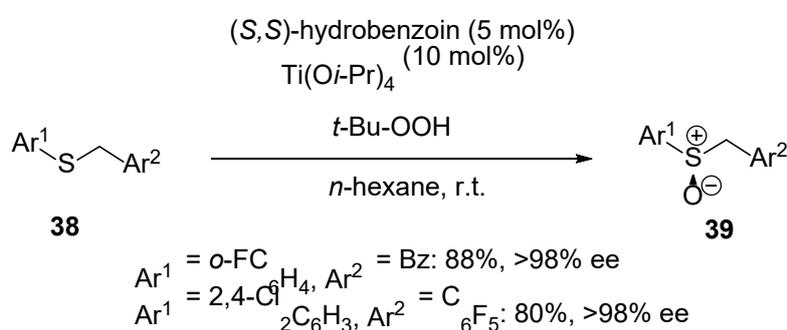
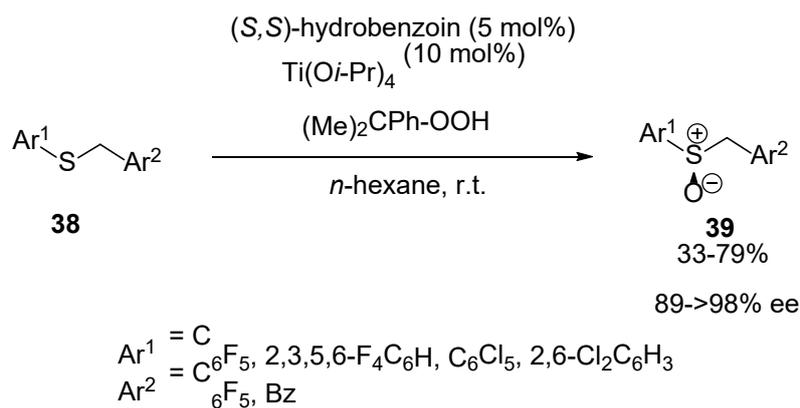
high yields (65-84%). When the complete fluorination was reserved to the aryl moiety of the sulfide, as in 2,4-dichlorobenzyl pentafluorophenyl sulfide ( $\text{Ar}^1 = \text{C}_6\text{F}_5$ ,  $\text{Ar}^2 = 2,4\text{-Cl}_2\text{C}_6\text{H}_3$ ) and 4-iodobenzyl pentafluorophenyl sulfide ( $\text{Ar}^1 = \text{C}_6\text{F}_5$ ,  $\text{Ar}^2 = p\text{-IC}_6\text{H}_4$ ), a slight decrease in enantioselectivity was observed since the corresponding sulfoxides were formed in 88% and 73% ee, respectively. Non-fluorinated compounds bearing iodine or bromide atoms ( $\text{Ar}^1 = p\text{-Tol}$ ,  $p\text{-BrC}_6\text{H}_4$ , Ph and  $\text{Ar}^2 = p\text{-IC}_6\text{H}_4$ ,  $p\text{-BrC}_6\text{H}_4$ , Ph) as well as unsubstituted substrate ( $\text{Ar}^1 = \text{Ar}^2 = \text{Ph}$ ), all provided remarkable enantioselectivities (95->98% ee). In the sole case of a substrate exhibiting an hydroxyl function on the aryl group ( $\text{Ar}^1 = o\text{-HOCH}_2\text{C}_6\text{H}_4$ ,  $\text{Ar}^2 = \text{Ph}$ ), a low enantioselectivity (29% ee) was obtained albeit combined with a good yield (74%). This could be related to the close proximity of the hydroxyl function to the sulfur atom that changed the coordination mode of the sulfide to the titanium catalyst.



**Scheme 23.** Oxidation of aryl benzyl sulfides in the presence of (S,S)-hydrobenzoin [65].

When applying these conditions to a pentafluorobenzyl pentafluorophenyl sulfide ( $\text{Ar}^1 = \text{Ar}^2 = \text{C}_6\text{F}_5$ ), the authors obtained a moderate enantioselectivity (61% ee) combined with a low

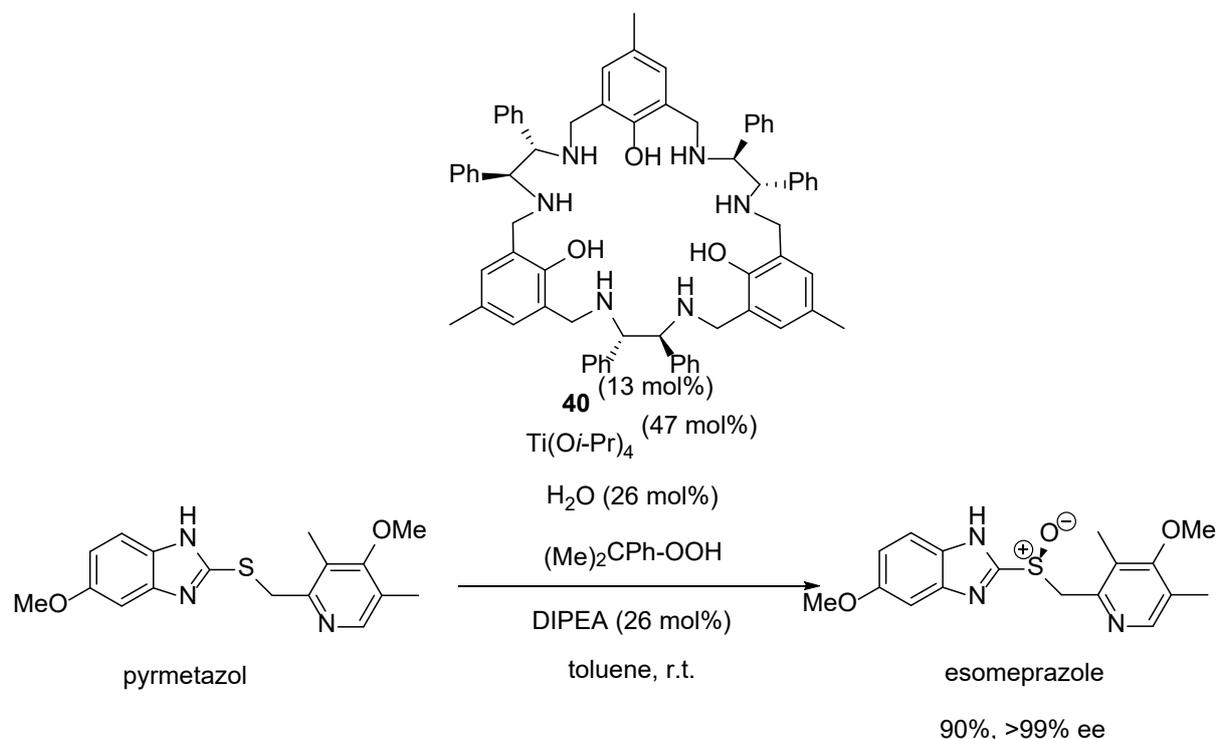
yield (19%). Later, they found that using cumene hydroperoxide instead of *tert*-butyl hydroperoxide as oxidant under the same reaction conditions allowed a spectacular increase in the enantioselectivity of the process (>98% ee) which provided the corresponding product in 76% yield (Scheme 24) [66]. These conditions were applicable to another fluorinated substrate ( $\text{Ar}^1 = 2,3,5,6\text{-F}_4\text{C}_6\text{H}$ ,  $\text{Ar}^2 = \text{C}_6\text{F}_5$ ), which led to the corresponding sulfoxide with the same enantioselectivity (98% ee) and comparable yield (79%) both much higher than those obtained by using *tert*-butyl hydroperoxide as oxidant (36% ee, 16% yield) [67]. Comparable results were also achieved in the formation of chlorinated sulfoxides ( $\text{Ar}^1 = \text{C}_6\text{Cl}_6$  or  $2,6\text{-Cl}_2\text{C}_6\text{H}_3$ ,  $\text{Ar}^2 = \text{C}_6\text{F}_5$ ) which were obtained in high enantioselectivities (89-93% ee) and moderate yields (33-51%). Moreover, a pentafluorophenyl phenacyl sulfide ( $\text{Ar}^1 = \text{C}_6\text{F}_5$ ,  $\text{Ar}^2 = \text{Bz}$ ), also underwent oxidation with cumene hydroperoxide to give the corresponding enantiopure (>98% ee) product in 58% yield. Other aryl phenacyl sulfides ( $\text{Ar}^1 = o\text{-CFC}_6\text{H}_3$ ,  $\text{Ar}^2 = \text{Bz}$  and  $\text{Ar}^1 = 2,4\text{-Cl}_2\text{C}_6\text{H}_3$ ,  $\text{Ar}^2 = \text{C}_6\text{F}_5$ ) were also investigated under these conditions but in these cases better results were achieved by switching from cumene hydroperoxide to *tert*-butyl hydroperoxide (Scheme 24). Indeed, the corresponding enantiopure (>98% ee) products were obtained in 80-88% yields by employing *tert*-butyl hydroperoxide as the oxidant while much lower enantioselectivities of 33-57% ee albeit combined with high yields (83-84%) were observed with cumene hydroperoxide.



**Scheme 24.** Oxidations of perfluorinated aryl benzyl sulfides and arylphenacyl sulfides in the presence of (*S,S*)-hydrobenzoin [66,67].

Along with 1,2-diols, other types of chiral ligands have been investigated in these reactions, such as chiral macrocycles. As shown in Scheme 25, macrocycle **40** derived from 2,6-diformyl-4-methylphenol and (*S,S*)-1,2-diphenylethylenediamine was investigated in 2015 by Zhou et al. in the asymmetric titanium-catalyzed oxidation of pyrimetazol with the aim of synthesizing proton pump inhibitor esomeprazole [68]. The use of this ligand allowed this important product to be achieved enantiopure (>99% ee) with an excellent yield (90%). This remarkable result was obtained by using at room temperature 13 mol% of this ligand in combination with 47 mol% of Ti(Oi-Pr)<sub>4</sub> in the presence of 26 mol% of water and DIPEA as

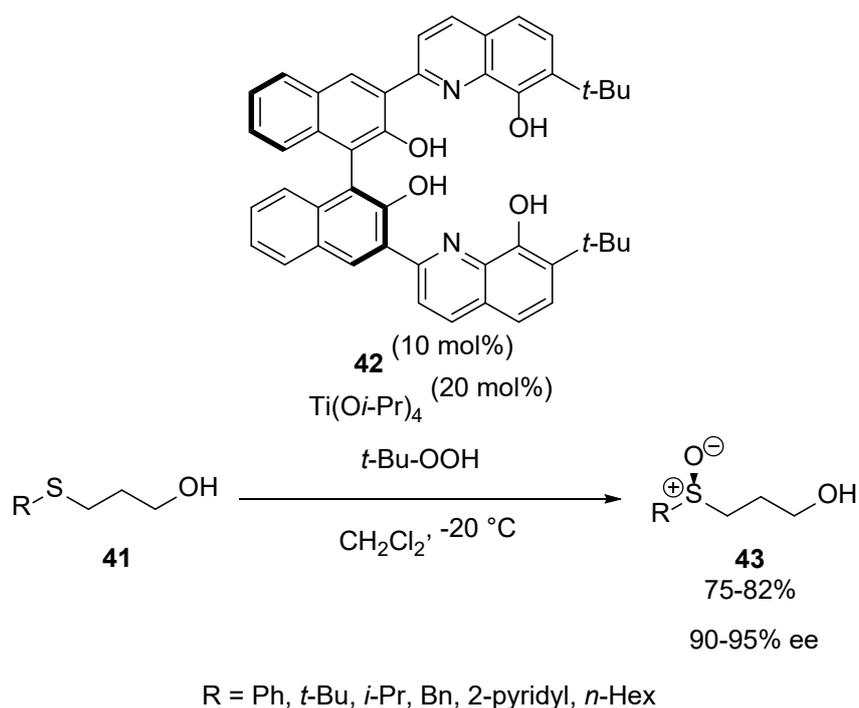
additives. The process employed toluene as the solvent and cumene hydroperoxide as the oxidant.



**Scheme 25.** Oxidation of pyrimetazol into esomeprazole in the presence of macrocyclic ligand **40** [68].

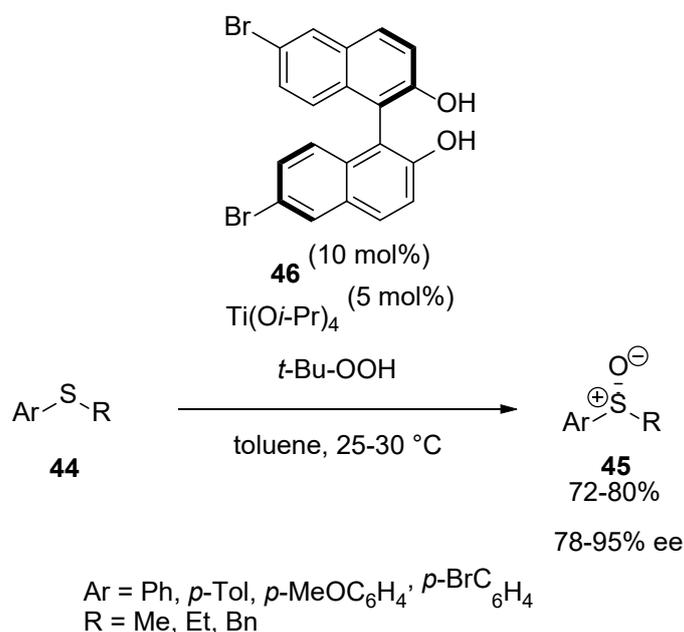
BINOL derivatives have also encountered success in these reactions [69]. For example, a new class of this type of ligands was introduced by Yamamoto and Bhadra in 2015 to be applied to promote asymmetric sulfoxidation of  $\gamma$ -hydroxypropyl sulfides **41** [70]. It concerned chiral tethered 8-quinolinol-based ligand **42** which generated in the presence of  $\text{Ti(Oi-Pr)}_4$  a bimetallic titanium complex with one metal center chelating to the hydroxy function of the substrate, and the other titanium center supplying the oxidant to the sulfide atom of the homoallylic alcohol. As depicted in Scheme 26, the oxidation of a diverse range

of  $\gamma$ -hydroxypropyl sulfides **41** with *tert*-butyl hydroperoxide performed at room temperature in dichloromethane as the solvent in the presence of 20 mol% of  $\text{Ti}(\text{O}i\text{-Pr})_4$  and 10 mol% of novel chiral ligand **42** led to the corresponding chiral sulfoxides **43** in both high yields (75-82%) and enantioselectivities (90-95% ee).



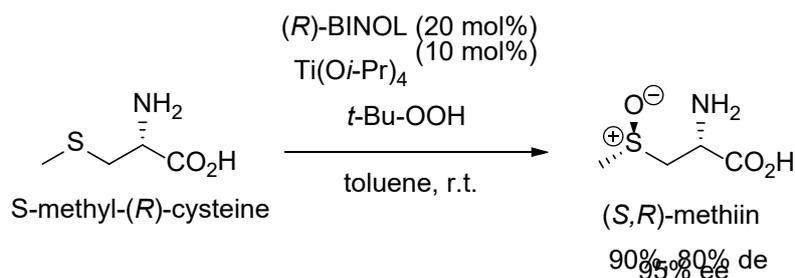
**Scheme 26.** Oxidation of  $\gamma$ -hydroxypropyl sulfides in the presence of tethered 8-quinolinol-based ligand **42** [70].

Later in 2020, Maddireddy et al. investigated the asymmetric oxidation of aryl alkyl sulfides **44** into the corresponding chiral sulfoxides **45** in the presence of a combination of 10 mol% of (*R*)-6,6'-dibromo-BINOL **46** as ligand and 5 mol% of  $\text{Ti}(\text{O}i\text{-Pr})_4$  as precatalyst [71]. The reaction was performed at 25-30 °C in toluene as the solvent, using *tert*-butyl hydroperoxide as the oxidant (Scheme 27). It afforded a range of chiral aryl alkyl sulfoxides **45** in good yields (72-80%) and high enantioselectivities (78-95% ee).



**Scheme 27.** Oxidation of aryl alkyl sulfides in the presence of (*R*)-BINOL-derived ligand **46** [71].

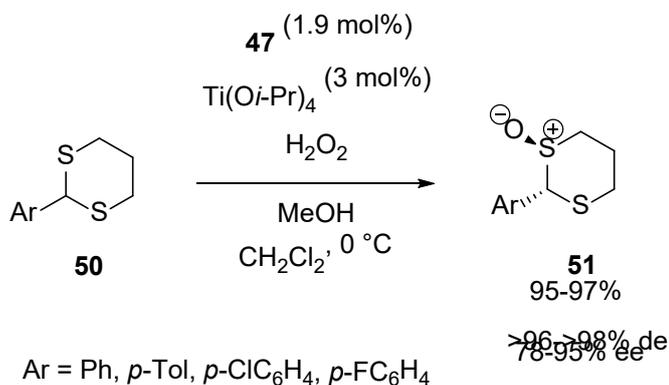
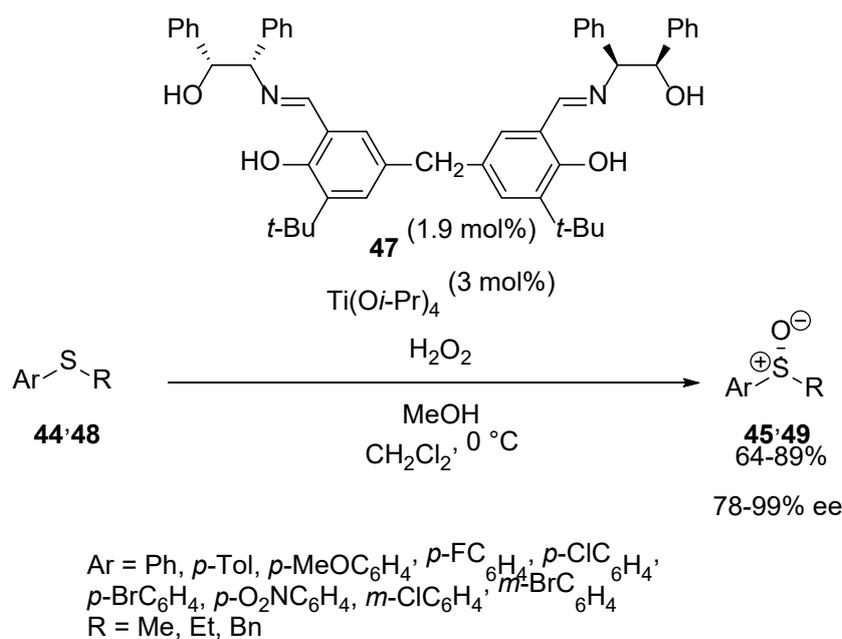
The same year, Kolodiaznyy et al. reported the synthesis of natural product (*1R,2S*)-methiin based on the asymmetric sulfoxidation of *S*-methyl-(*R*)-cysteine catalyzed by 20 mol% of (*R*)-BINOL and 10 mol% of Ti(Oi-Pr)<sub>4</sub> [72]. By using *tert*-butyl hydroperoxide as oxidant in toluene as solvent at room temperature, the product was obtained in a high yield (90%) and both high diastereo- and enantioselectivities (80% de, 95% ee), as illustrated in Scheme 28.



**Scheme 28.** Oxidation of S-methyl-(*R*)-cysteine in the presence of (*R*)-BINOL [72].

### 3.2. With hydrogen peroxide as oxidant

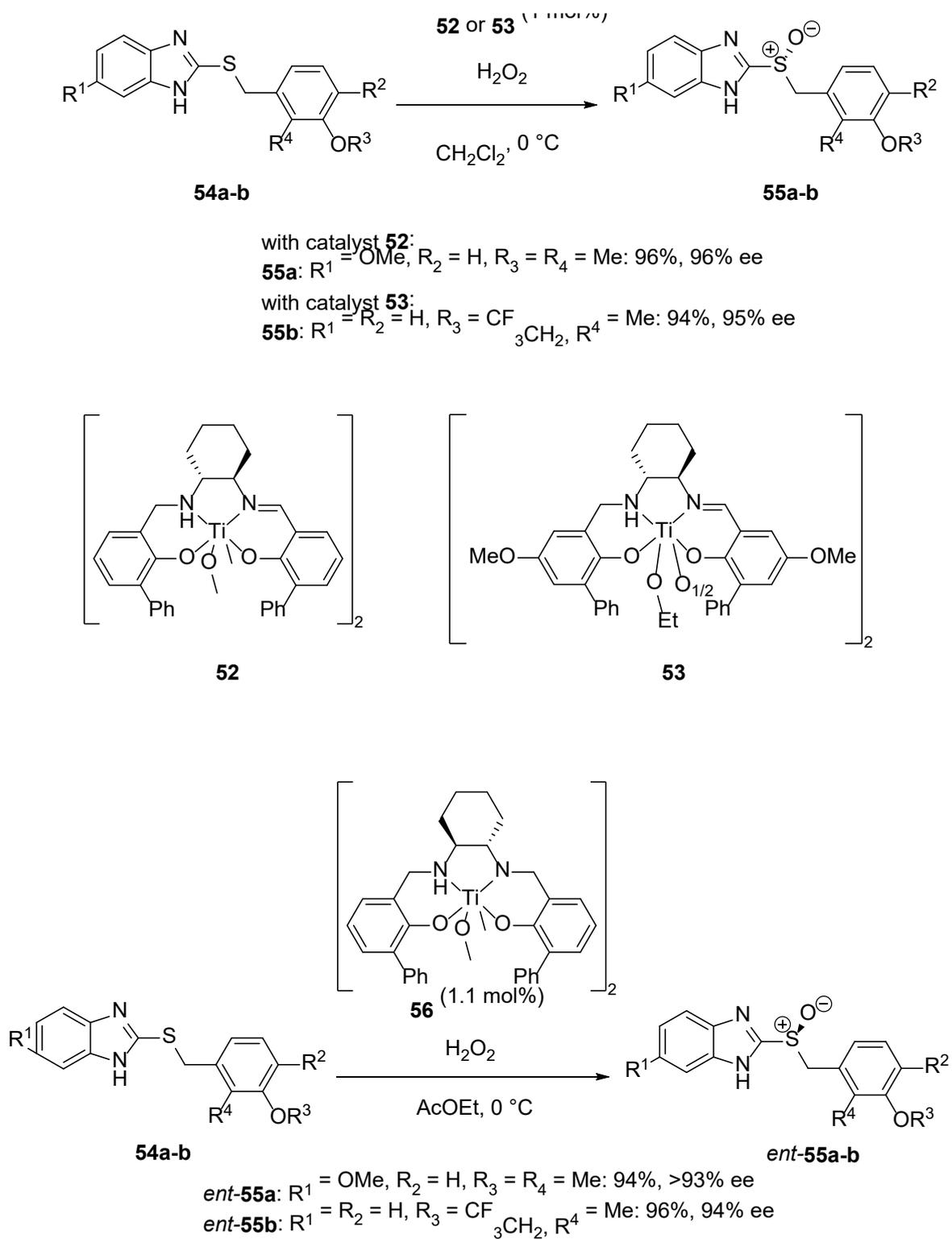
In contrast with alkyl hydroperoxides which are expensive, toxic and hazardous reagents, the use of cheaper and greener oxidants, such as hydrogen peroxide, is more challenging [73]. Indeed, environmentally benign hydrogen peroxide is a preferred oxidant and has been widely applied in asymmetric titanium-catalyzed oxidation of sulfides, especially in the presence of salen-, salan- or Schiff base-derived ligands. In an example reported in 2015 by Abdi and Bajaj, a series of novel dimeric Schiff base ligands derived from chiral amino alcohols were investigated in asymmetric titanium-catalyzed sulfoxidations with hydrogen peroxide as oxidant [74]. Among them, ligand **47**, with a chirality arisen from chiral 2-amino-1,2-diphenylethanol, was found optimal to promote at only 1.9 mol% of catalyst loading combined with 3 mol% of Ti(*Oi*-Pr)<sub>4</sub> in dichloromethane as the solvent the asymmetric oxidation of a range of aryl alkyl sulfides **44,48** into the corresponding chiral sulfoxides **45,49** (Scheme 29). The latter were synthesized at 0 °C in the presence of methanol as an additive with good to high yields (64-89%) and uniformly high enantioselectivities (78-99% ee). The catalytic system could be applied to the oxidation of cyclic dithioacetals **50** which afforded the corresponding sulfoxides **51** in remarkable yields (95-97%) and diastereoselectivities (>96->98% de) combined with high enantioselectivities (78-95% ee), as shown in Scheme 29.



**Scheme 29.** Oxidations of sulfides and cyclic dithioacetals in the presence of dimeric Schiff base ligand **47** [74].

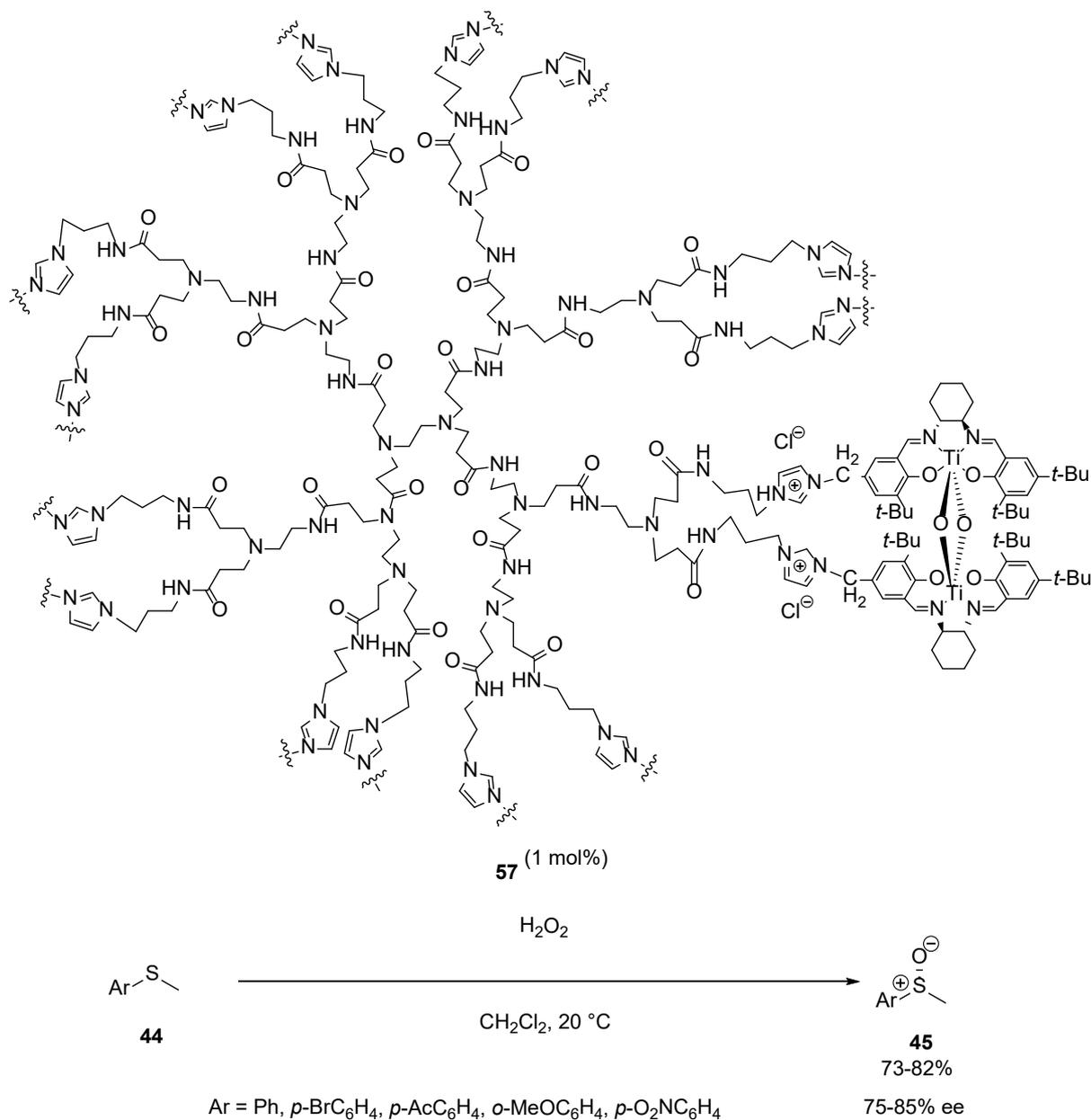
With the aim of synthesizing proton pump inhibitors (*S*)-omeprazole and (*R*)-lansoprazole, Bryliakov et al. investigated in 2015 dinuclear titanium (*R,R*)-salanen catalysts **52** and **53** in the asymmetric oxidation of the corresponding pyridylmethylthiobenzimidazoles **54a-b** with hydrogen peroxide [75]. As presented in Scheme 30, the reactions were performed at 0 °C in dichloromethane as the solvent by using only 1 mol% of catalyst **52** or **53**. (*R*)-Omeprazole **55a** was synthesized in the presence of catalyst **52** with 96% yield and 96% ee while (*R*)-lansoprazole **55b** was obtained in 94% yield and 95% ee by using catalyst **53**. Later in 2017,

these authors investigated the same reactions in the presence of the corresponding (*S,S*)-salan titanium catalyst **56** [76]. In this case, the best results were achieved by performing the reaction in ethyl acetate as the solvent in the presence of 1.1 mol% of catalyst **56** (Scheme 30). Performed at 0 °C, the oxidation of pyridylmethylthiobenzimidazole **54a** led to (*S*)-omeprazole *ent*-**55a** in 94% yield and >93% ee while that of pyridylmethylthiobenzimidazole **54b** afforded (*S*)-lansoprazole *ent*-**55b** in almost similar excellent yield (96%) and enantioselectivity (94% ee).



**Scheme 30.** Oxidations of pyridylmethylthiobenzimidazoles in the presence of dinuclear titanium salalen/salan catalysts **52**, **53** and **56** [75,76].

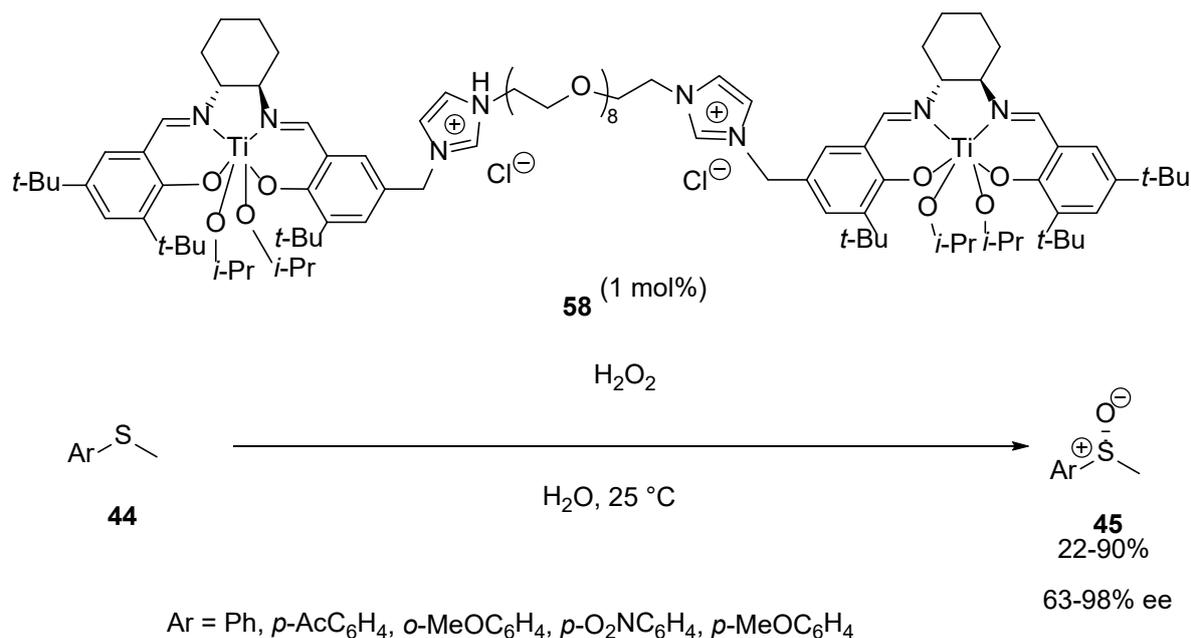
In 2015, Yin and Tan described the synthesis of novel reusable chiral dendritic Ti(IV)–salen catalyst **57** by the covalent confinement of multiple chiral salen titanium(IV) complexes on the periphery of a polyamidoamine dendrimer through a flexible ionic liquid linker [77]. Using 1 mol% of this catalyst in dichloromethane as solvent at 0 °C allowed methyl aryl sulfides **44** to be oxidized by hydrogen peroxide into the corresponding chiral sulfoxides **45** with both high enantioselectivities (75-85% ee) and yields (73-82%), as illustrated in Scheme 31. This catalyst provided higher enantioselectivities than the corresponding neat complex ( $\leq 68\%$  ee).



**Scheme 31.** Oxidation of methyl aryl sulfides in the presence of dendritic salen titanium(IV) catalyst **57** [77].

The same authors also developed another reusable chiral dinuclear Ti(IV)–salen catalyst **58** in which two Ti(IV)–salen units were connected with various polyethylene glycol-based dicationic ionic liquid linkers [78]. The latter was investigated at 1 mol% of catalyst loading in the same oxidation of methyl aryl sulfides **44** performed at 25 °C in water, leading to chiral

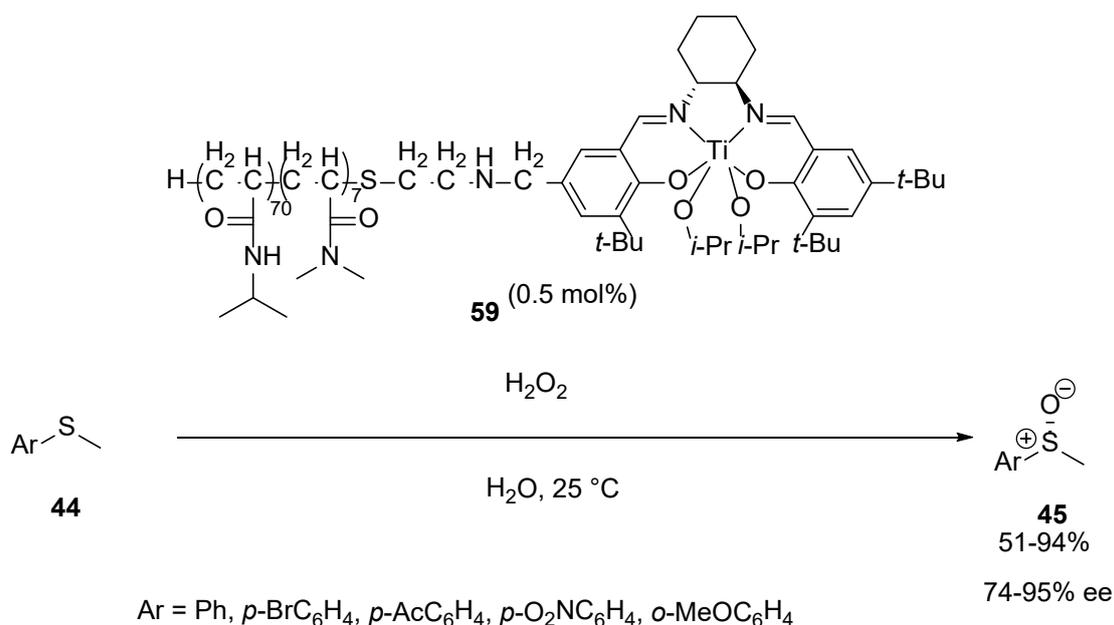
sulfoxides **45** in low to excellent yields (22-90%) and moderate to very high enantioselectivities (63-98% ee), as shown in Scheme 32. The enantioselectivity and the catalytic efficiency were found significantly higher than those obtained by using the corresponding neat complex ( $\leq 16\%$  yield and  $\leq 79\%$  ee).



**Scheme 32.** Oxidation of methyl aryl sulfides in water in the presence of polyethylene glycol-based dinuclear salen titanium(IV) catalyst **58** [78].

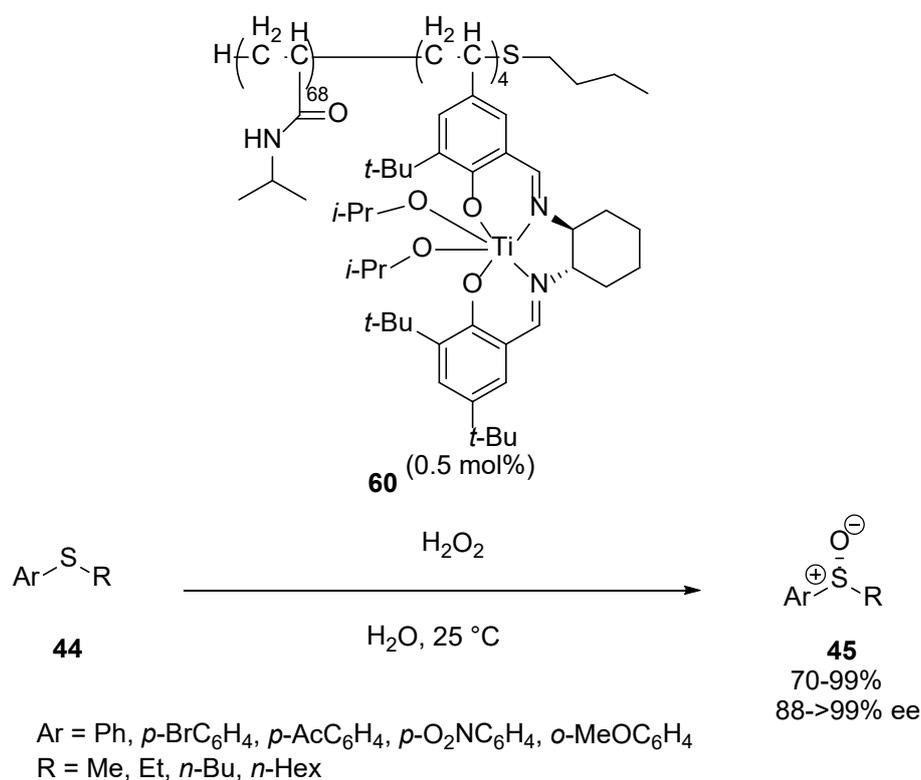
In the same area, these authors also investigated these reactions by using a novel thermo-responsive amphiphilic copolymer of poly(*N*-isopropylacrylamide-co-*N,N*-dimethyl acrylamide) **59** [79]. As depicted in Scheme 33, the oxidation of several aryl methyl sulfides **44** into chiral sulfoxides **45** was performed in water at 25 °C in the presence of only 0.5 mol% of catalyst **59** with both good to excellent yields (51-94%) and enantioselectivities (74-95% ee). The catalyst could be easily recovered by thermo-controlled separation and reused for

several cycles. Again, the corresponding neat complex was found to be far less efficient ( $\leq 9\%$  conversion and 79% ee).



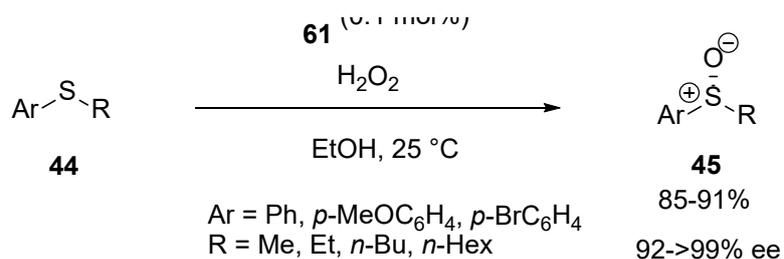
**Scheme 33.** Oxidation of aryl methyl sulfides in water in the presence of copolymer of poly(*N*-isopropylacrylamide-*co*-*N,N*-dimethyl acrylamide)-based salen titanium(IV) catalyst **59** [79].

These authors also reported the synthesis of a novel single-chain polymeric nanoparticles **60** containing a chiral Ti(IV)-salen complex in a hydrophobic cavity [80]. This catalyst behaved as an enzyme-mimetic catalyst for the enantioselective oxidation of alkyl aryl sulfides **44** with hydrogen peroxide performed in water, providing the corresponding chiral sulfoxides **45** with uniformly excellent enantioselectivities (88->99% ee) and good to quantitative yields (70-99%), as presented in Scheme 34. The catalyst could be recovered by thermo-controlled separation.

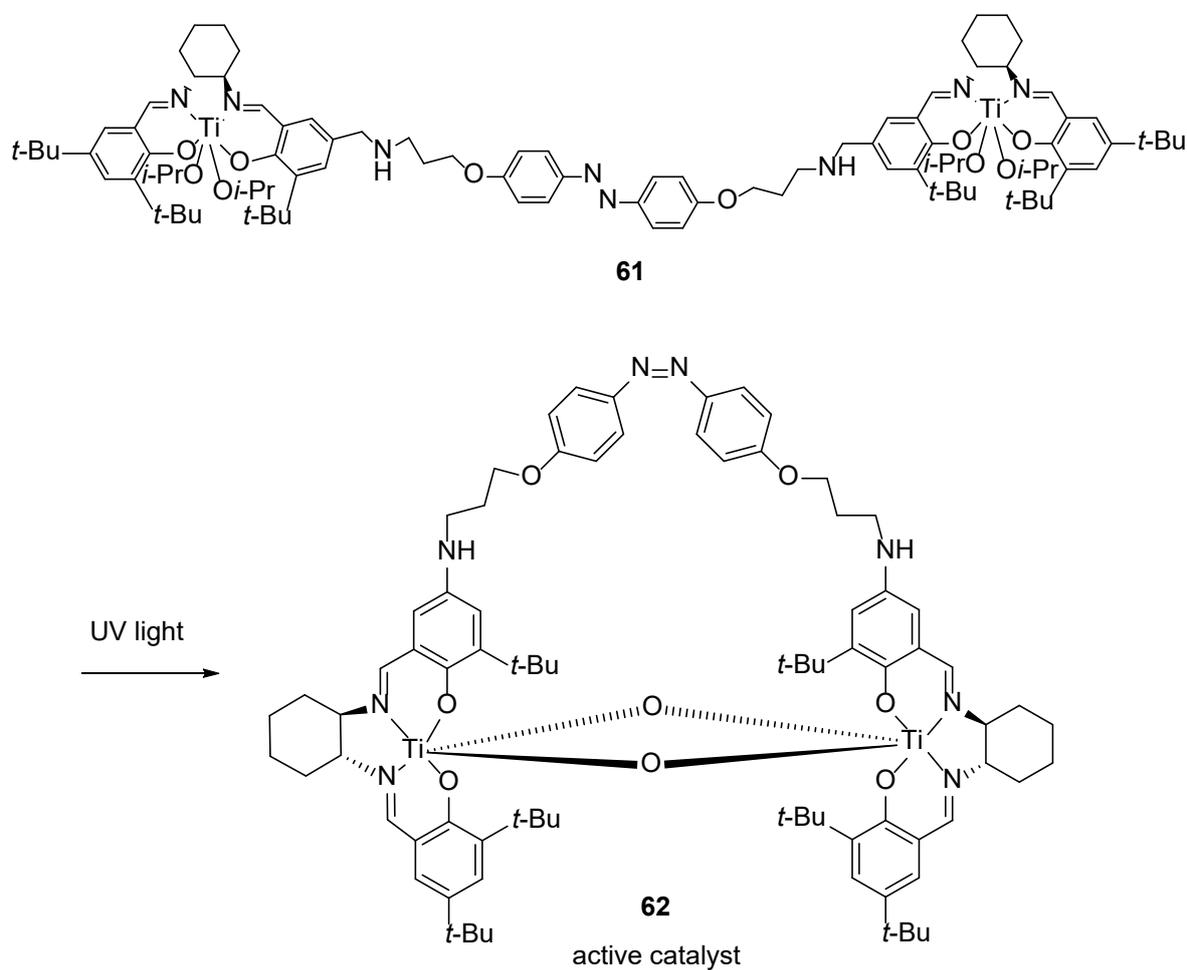


**Scheme 34.** Oxidation of aryl alkyl sulfides in water in the presence of polymeric nanoparticles containing a salen titanium(IV) catalyst **60** [80].

In 2020, these authors bridged two titanium(salen)units with an azobenzene linker to generate novel bimetallic catalyst **61** to be used in asymmetric sulfoxidation [81]. Under UV irradiation, this complex changed the spatial arrangement of the two catalytic active units through *trans/cis* photoisomerization of the azobenzene moiety, leading to the cooperative bimetallic catalyst **62** as single *cis*-isomer, which was the real catalytic species of the sulfoxidation reaction. Through this cooperative catalysis in situ generated under UV irradiation, several alkyl aryl sulfides **44** could be oxidized at 25 °C into chiral sulfoxides **45** in ethanol as the solvent with both excellent yields (85-91%) and enantioselectivities (92->99% ee), as shown in Scheme 35.



generation of active catalyst **62**:

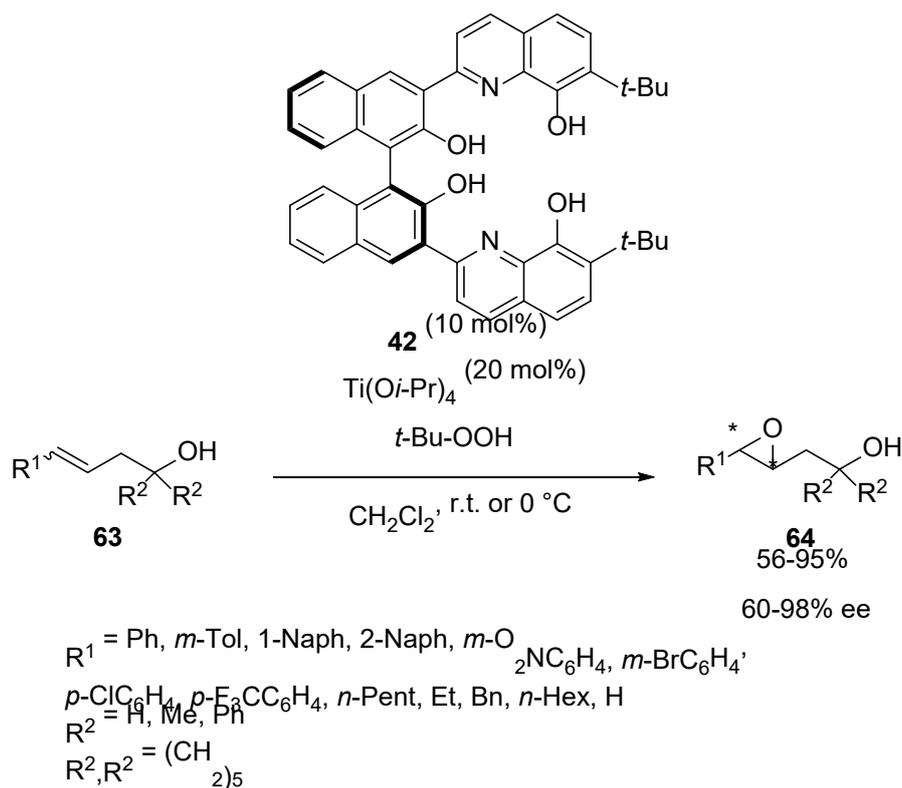


**Scheme 35.** Oxidation of aryl alkyl sulfides in the presence of photoswitchable cooperative dinuclear salen titanium(IV) catalyst **61** [81].

## 4. Enantioselective titanium-catalyzed epoxidations

### 4.1. With alkyl hydroperoxides as oxidants

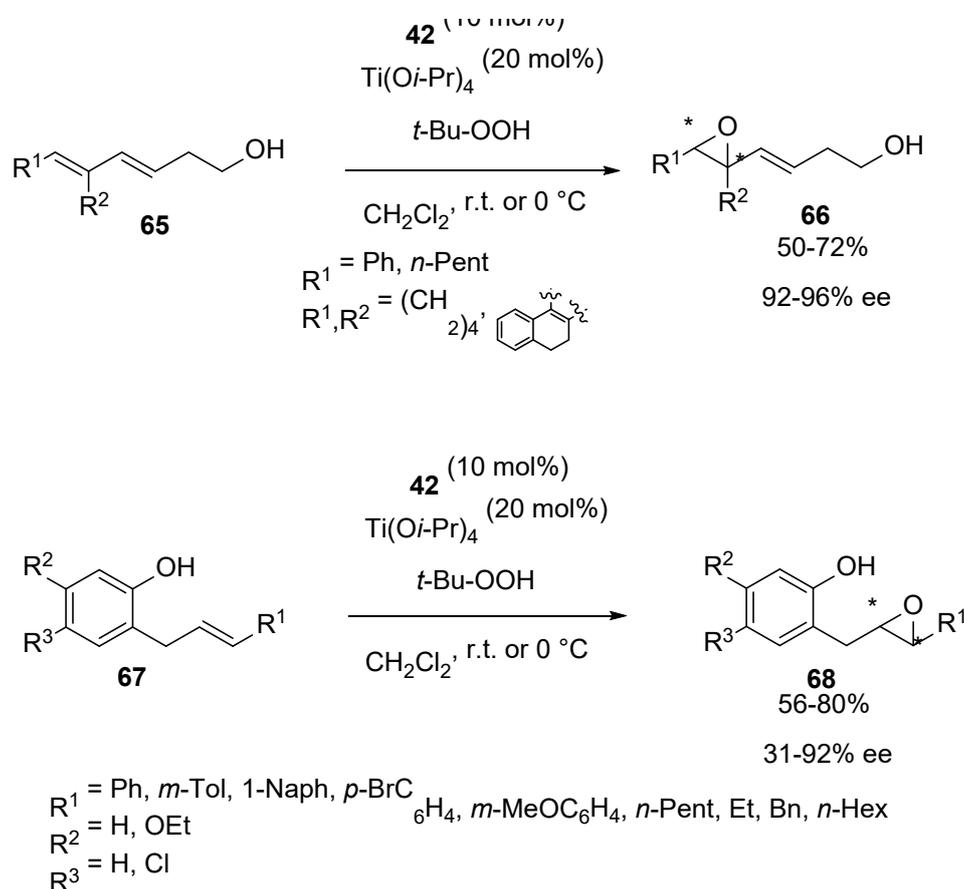
Epoxides constitute key intermediates in organic synthesis and are widely present in natural and biologically active products [82]. Early introduced by Katsuki and Sharpless in 1980s [83], the enantioselective titanium-catalyzed oxidation of allylic alcohols performed with *tert*-butyl hydroperoxide as oxidant in the presence of tartrate chiral ligands is still considered as the most employed methodology to synthesize chiral epoxides [84]. In 2015, a new class of chiral ligands was introduced by Yamamoto and Bhadra to be applied in asymmetric epoxidation of homoallylic alcohols **63** [70]. Among them, chiral tethered 8-quinolinol-based ligand **42** was found to generate in the presence of  $\text{Ti}(\text{O}i\text{-Pr})_4$  a dinuclear titanium complex with one metal center chelating to the hydroxy function of the substrate, and the other titanium center supplying the oxidant to the reactive olefin site of the homoallylic alcohol. As depicted in Scheme 36, the oxidation of a range of primary and tertiary homoallylic alcohols **63** with *tert*-butyl hydroperoxide performed generally at room temperature in dichloromethane as the solvent in the presence of 20 mol% of  $\text{Ti}(\text{O}i\text{-Pr})_4$  and 10 mol% of novel chiral ligand **42** led to the corresponding chiral epoxides **64** in both good to excellent yields (56-95%) and enantioselectivities (60-98% ee).



**Scheme 36.** Epoxidation of homoallylic alcohols in the presence of tethered 8-quinolinol-based ligand **42** [70].

The same reaction conditions were applied to the asymmetric epoxidation of conjugated homoallylic alcohols **65** [70]. As shown in Scheme 37, the enantioselective epoxidation occurred regioselectively at the proximal double bond, leading to chiral epoxy-alkenols **66** in good yields (50-72%) and uniformly excellent enantioselectivities (92-97% ee). Furthermore, 2-allylic phenols **67** could also be oxidized under the same conditions to give the corresponding chiral epoxides **68** in good to high yields (56-80%) and low to high enantioselectivities (31-92% ee). Aryl-substituted substrates ( $R^1 = \text{aryl}$ ), which could bear functional groups on both of the phenyl rings, all provided enantioselectivities  $\geq 81\%$  ee while the presence of an aliphatic substituent ( $R^1 = n\text{-Pent}$ ) in the allylic side chain dropped the

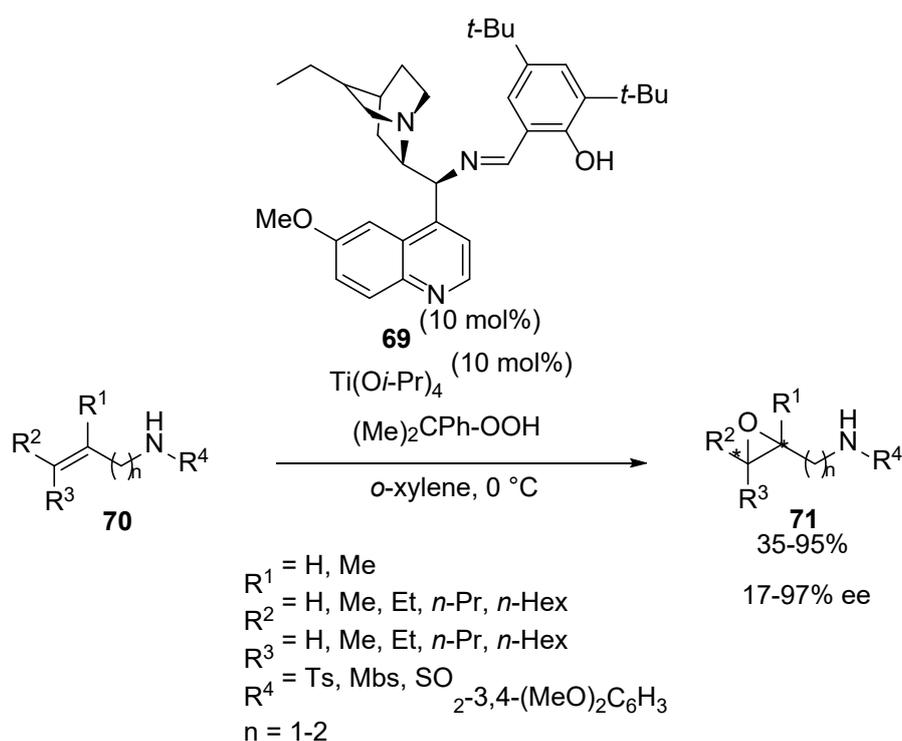
enantioselectivity (31% ee). This result was probably related to the flexibility of the aliphatic chain, allowing the catalyst to oxidize both faces of the alkene.



**Scheme 37.** Epoxidations of conjugated homoallylic alcohols and 2-allylic phenols in the presence of tethered 8-quinolinol-based ligand **42** [70].

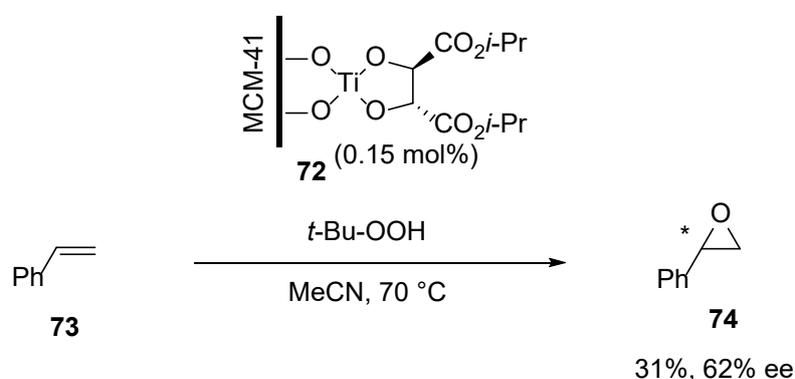
Later in 2016, He and co-workers developed novel chiral Schiff base ligands derived from cinchona alkaloids to be investigated in asymmetric epoxidation [85]. Among them, ligand **69** derived from hydroquinine was found optimal in enantioselective titanium-catalyzed epoxidation of *N*-alkenyl sulfonamides, such as Ts- and Mbs-protected allylic ( $n = 1$ ) and homoallylic ( $n = 2$ ) amine derivatives **70**, with cumene hydroperoxide. The reaction, performed at 0 °C in *o*-xylene as solvent with 10 mol% of titanium catalyst in situ generated

from ligand **69** and  $\text{Ti}(\text{O}i\text{-Pr})_4$ , provided access to chiral epoxy sulfonamides **71** in moderate to high yields (35-95%) and low to excellent enantioselectivities (17-97% ee), as presented in Scheme 38. The lowest enantioselectivities (17-29% ee) were obtained in the reaction of 2-disubstituted allylic amides ( $\text{R}^1 \neq \text{H}$ ,  $n = 1$ ) probably due to steric hindrance. Surprisingly, the reaction of *cis*-alkenes provided better enantioselectivities and yields than the corresponding *trans*-alkenes. Considering that a number of bioactive products, including antibacterial and antiviral agents, are prepared from chiral epoxides exhibiting an amine moiety as building blocks, this simple novel methodology was attractive.



**Scheme 38.** Epoxidation of *N*-alkenyl sulfonamides in the presence of hydroquinine-derived Schiff base ligand **69** [85].

It must be noted that few examples of asymmetric epoxidation using heterogeneous chiral titanium catalysts have been described so far [86]. Among them, MCM-41-supported tartrate titanium catalyst **72** was investigated by Fraile and Fadhli in the epoxidation of styrene **73** with *tert*-butyl hydroperoxide [87]. As illustrated in Scheme 39, the process carried out at 70 °C in acetonitrile as the solvent led to the corresponding chiral epoxide **74** in 31% yield and 62% ee. The catalyst was prepared by grafting  $\text{Ti}(\text{O}i\text{-Pr})_4$  on the surface of MCM-41. Then, the titanium sites of Ti-MCM-41 were modified with (*R,R*)-diisopropyl tartrates.

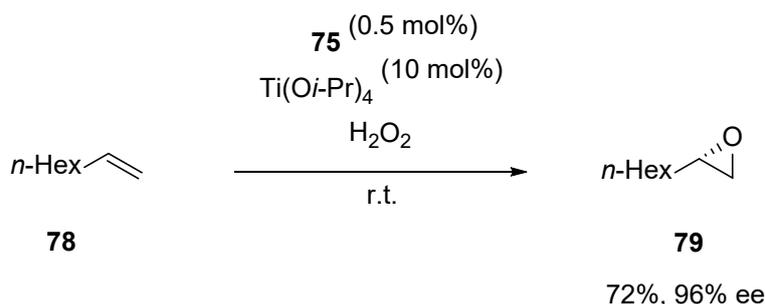
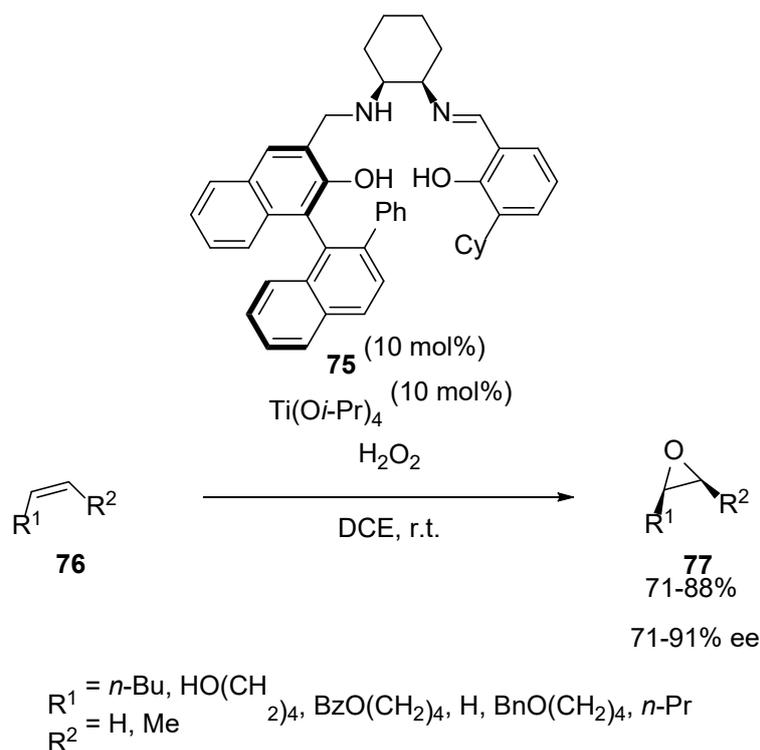


**Scheme 39.** Epoxidation of styrene in the presence of MCM-41-supported tartrate titanium catalyst **72** [87].

#### 4.2. With hydrogen peroxide as oxidant

It is only in 2005 that an enantioselective titanium-catalyzed epoxidation using environmentally friendly hydrogen peroxide as oxidant was described by Katsuki et al. [88]. Enantioselectivities of up to >99% ee were achieved by using a chiral bis( $\mu$ -oxido) titanium(IV) salanen complex. Ever since, many titanium complexes derived from other chiral salanen [89] and salan ligands [90] have been successfully applied to promote these reactions.

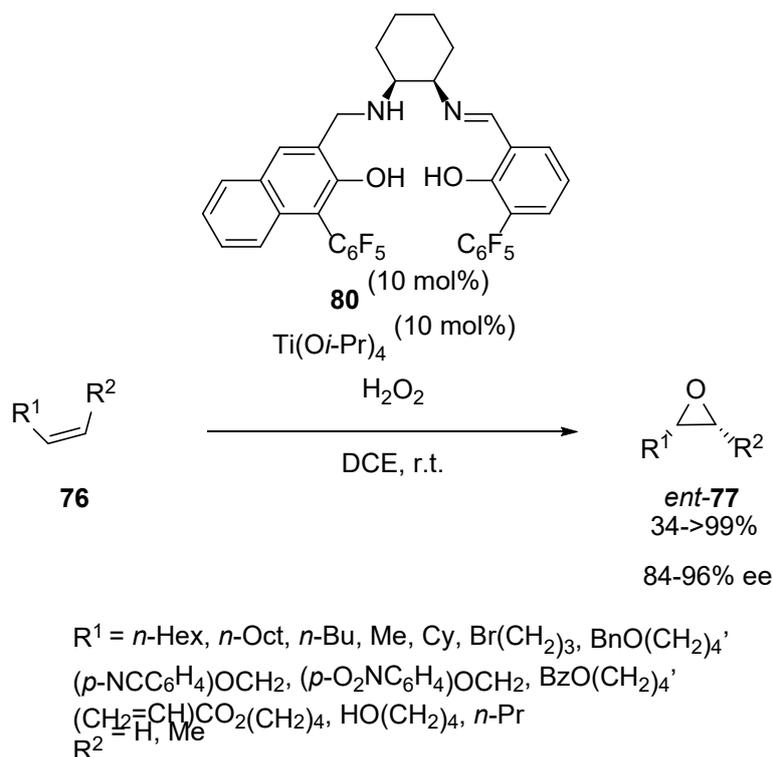
Among them, novel salanen ligand **75** based on a *cis*-1,2-diaminocyclohexane was designed by Berkessel et al., in 2015 [91]. The corresponding titanium complex derived from Ti(*Oi*-Pr)<sub>4</sub> employed at 10 mol% of catalyst loading was found to promote at room temperature in DCE as solvent the epoxidation of terminal non-conjugated olefins and *cis*-1,2-disubstituted alkenes **76** into chiral epoxides **77** with both high yields (71-88%) and enantioselectivities (71-91% ee). Remarkably, the authors found that the epoxidation of 1-octene **78** could be performed under solvent-free conditions with only 0.5 mol% of the same catalyst, affording the corresponding almost enantiopure epoxide **79** (96% ee) in 72% yield (Scheme 40).



**Scheme 40.** Epoxidations of non-conjugated olefins in the presence of *cis*-salanen ligand **75** [91].

With the aim of discovering more accessible ligands, these authors designed in 2016 a new generation of readily available *cis*-salanen ligands derived from fluorinated salicyclic aldehyde derivatives and *cis*-1,2-diaminocyclohexane [92]. These ligands were investigated at 10 mol% of catalyst loading with the same quantity of  $\text{Ti(Oi-Pr)}_4$  in the same asymmetric epoxidation of terminal non-conjugated olefins and *cis*-1,2-disubstituted alkenes **76** with hydrogen peroxide in DCE as solvent (Scheme 41). Among them, ligand **80** was found optimal to achieve at room temperature chiral epoxides *ent*-**77** in homogeneous high enantioselectivities (84-96% ee) and moderate to quantitative yields (34->99%). Interestingly,

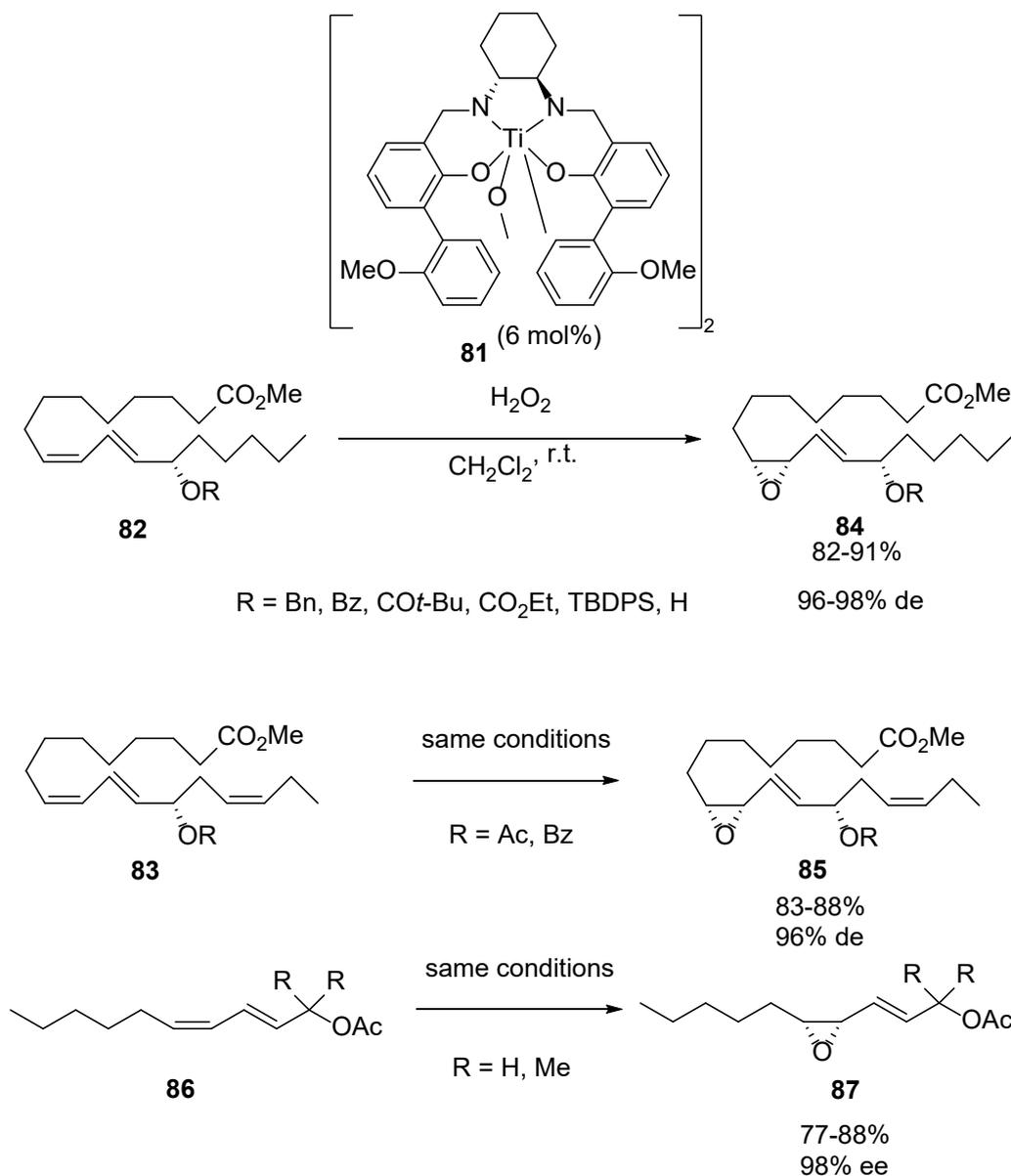
the authors showed that it was possible to decrease the catalyst loading to 0.5 mol% when pentafluorobenzoic acid (0.5 mol%) was used as an additive. Under these conditions, the oxidation of 1-decene ( $R^1 = n\text{-octyl}$ ,  $R^2 = \text{H}$ ) performed at room temperature in DCE as solvent provided the corresponding chiral epoxide in 81% yield and 96% ee. Moreover, the catalyst could be recovered and reused.



**Scheme 41.** Epoxidation of non-conjugated olefins in the presence of *cis*-salanen ligand **80** [92].

In order to prepare chiral allylic epoxides constituting versatile building blocks in synthesis, Falck et al. investigated asymmetric titanium-catalyzed monoepoxidation of conjugated dienes, in 2015 (Scheme 42) [93]. In the presence of 6 mol% of dinuclear salan titanium catalyst **81**, a range of conjugated dienes **82** and **83** were regio- and diastereoselectively monoepoxidized by treatment with hydrogen peroxide at room temperature in dichloromethane as solvent to give the corresponding chiral allylic *cis*-epoxides **84** and **85** in both excellent yields (82-91%) and diastereoselectivities (96-98% de). The epoxidation was highly specific for *Z*-olefins. A comparable stereoselectivity was observed in the

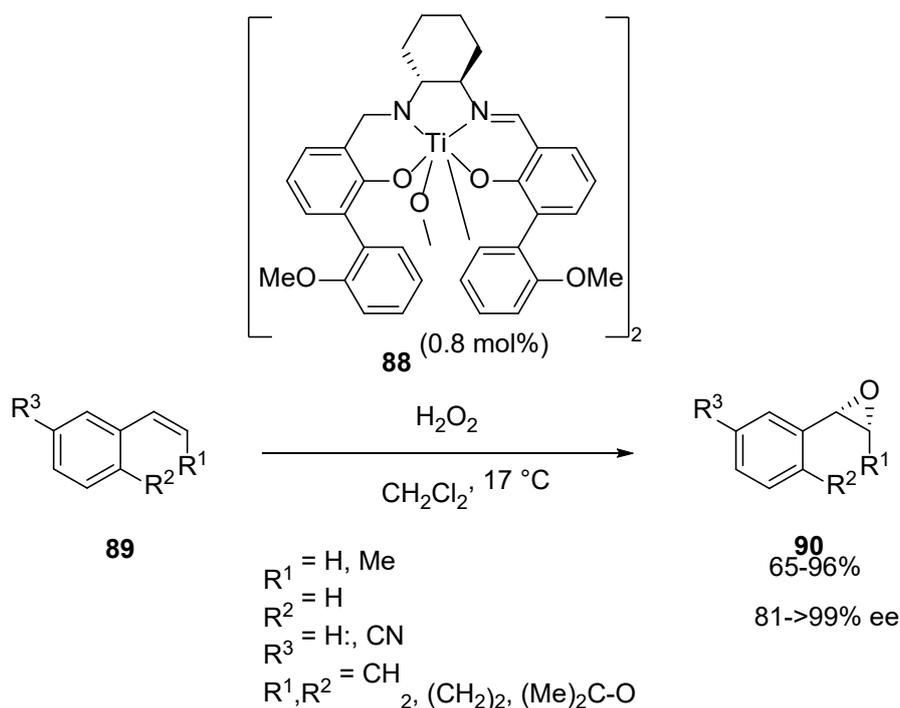
monoepoxidation of conjugated dienes **86** without an existing stereocenter which led to products **87** in 98% ee and high yields (77-88%).



**Scheme 42.** Epoxidations of conjugated dienes in the presence of dinuclear salanen titanium catalyst **81** [93].

The corresponding dinuclear salanen titanium catalyst **88** was synthesized by Bryliakov et al. in 2016 to be investigated as promotor in enantioselective epoxidation of conjugated olefins **89** [94]. When employed at only 0.8 mol% of catalyst loading in dichloromethane as

solvent at 17 °C, catalyst **88** allowed a range of chiral epoxides **90** to be achieved in uniformly high enantioselectivities (81->99% ee) and good to excellent yields (65-96%) from the corresponding acyclic and cyclic conjugated olefins **89** (Scheme 43). In this study, the authors compared the performance of this catalyst with the corresponding salan one **81**, finding that titanium salanen complex **88** was more active and efficient with similar or slightly lower enantioselectivity depending on the substrate.

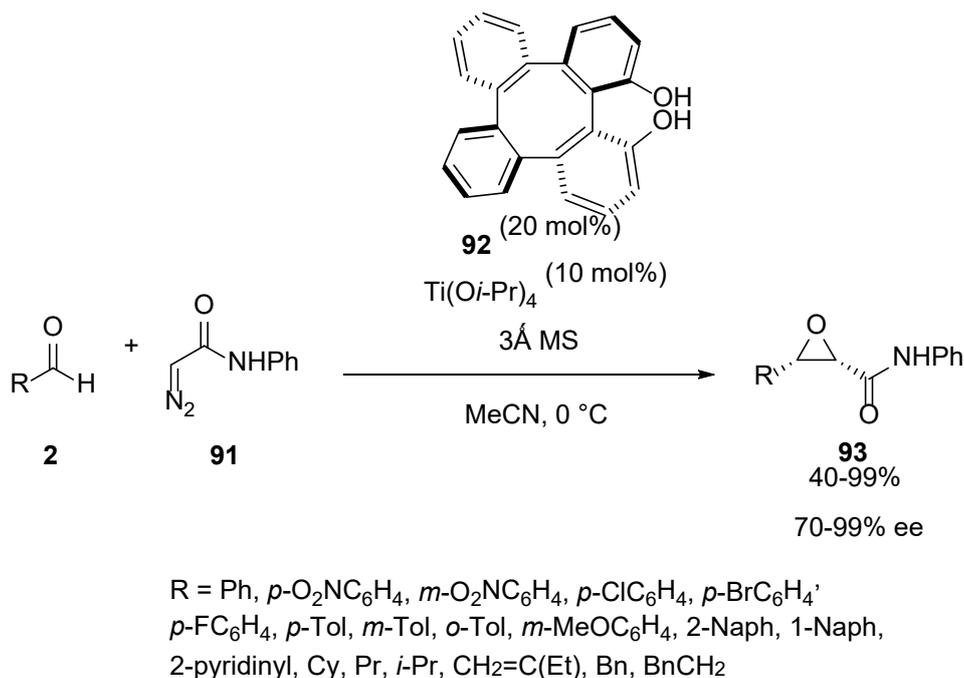


**Scheme 43.** Epoxidation of conjugated olefins in the presence of dinuclear salanen titanium catalyst **88** [94].

### 4.3. Darzens reactions

The Darzens reaction constitutes an alternative to the direct epoxidation of alkenes, allowing  $\alpha,\beta$ -epoxy carbonyl compounds to be synthesized from aldehydes [95]. In particular, this methodology has been applied to the synthesis of key synthetic building blocks, such as chiral glycidic amides, from aldehydes and diazoacetamides [96]. Previous reactions have been

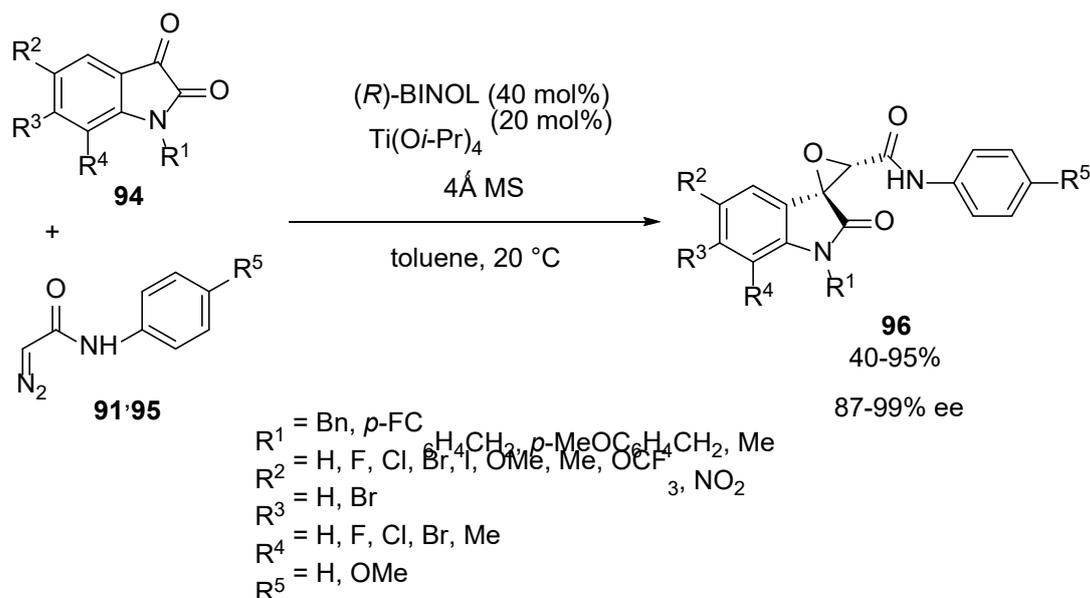
described with high enantioselectivity when promoted by titanium ligands, such as (*R*)-BINOL [97] or (+)-pinanediol [98]. In 2017, the reaction between aldehydes **2** and phenyl diazoacetamide **91** was reinvestigated by Wong et al. in the presence of a combination of 20 mol% of rigid (*R*)-1,16-dihydroxytetraphenylene ligand **92** and 10 mol% of Ti(O*i*-Pr)<sub>4</sub> [99]. Performed at 0 °C in acetonitrile as the solvent, the process led solely to chiral *cis*-glycidic amides **93** in both good to high yields (40-99%) and enantioselectivities (70-99% ee), as shown in Scheme 44. The catalyst system tolerated various aldehydes, including aromatic, heteroaromatic and aliphatic ones. Enantioselectivities were found  $\geq 92\%$  ee excepted in the reaction of *p*-fluorobenzaldehyde and *m*-tolualdehyde which provided 70-74% ee.



**Scheme 44.** Darzens reaction of aldehydes with phenyl diazoacetamide in the presence of (*R*)-1,16-dihydroxytetraphenylene ligand **92** [99].

The same authors disclosed the first asymmetric Darzens reaction of *N*-protected isatins **94** with diazoacetamides **91** and **95** which was performed in the presence of (*R*)-BINOL-derived titanium catalyst [100]. The latter was in situ generated at 20 °C from 40 mol% of (*R*)-BINOL

and 20 mol% of  $\text{Ti}(\text{O}i\text{-Pr})_4$  in toluene as solvent. The process allowed a simple synthesis of chiral spiro-epoxyoxindoles **96** as single diastereomers in good to excellent yields (40-95%) and high enantioselectivities (87-99% ee) regardless of the nature of the substituents exhibited by isatins (Scheme 45).

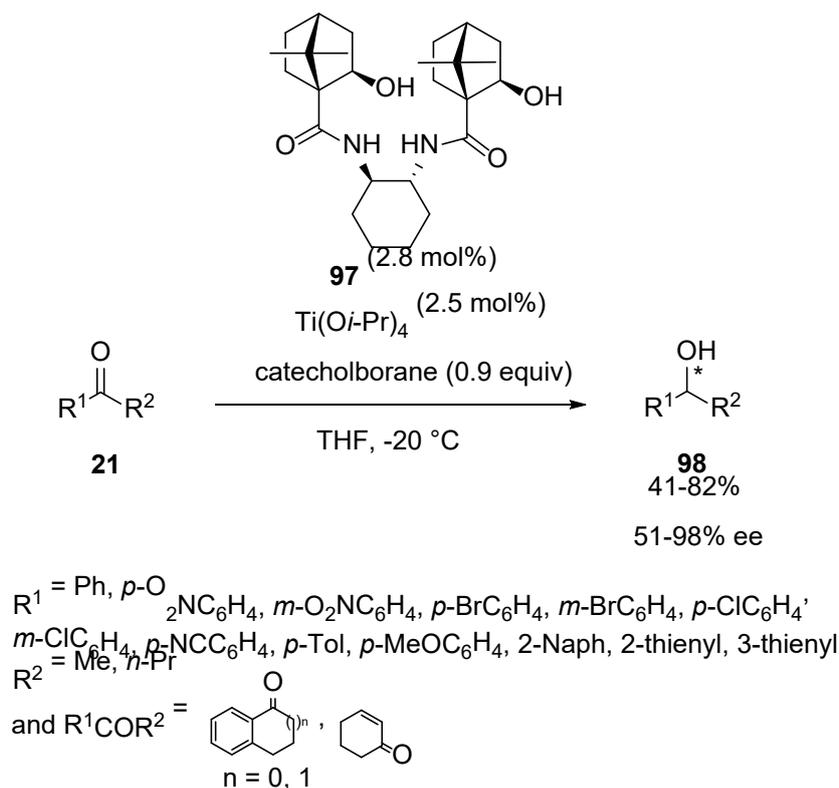


**Scheme 45.** Darzens reaction of isatins with diazoacetamides in the presence of (*R*)-BINOL [100].

## 5. Enantioselective titanium-catalyzed reduction reactions

Enantioselective reductions are common reactions in organic synthesis [101]. In 1994, Halterman and Buchwald developed the first asymmetric reductions of ketones catalyzed by chiral titanium complexes, such as titanocenes [102]. Ever since, other types of ligands mostly based on diols have been investigated in these reactions [103], such as  $\text{C}_2$ -symmetric chiral  $\beta$ -dihydroxyamide **97**, by Uang and Phothongkam in 2015 [104]. The use of only 2.8 mol% of this easily accessible ligand associated to 2.5 mol% of  $\text{Ti}(\text{O}i\text{-Pr})_4$  in the reduction of

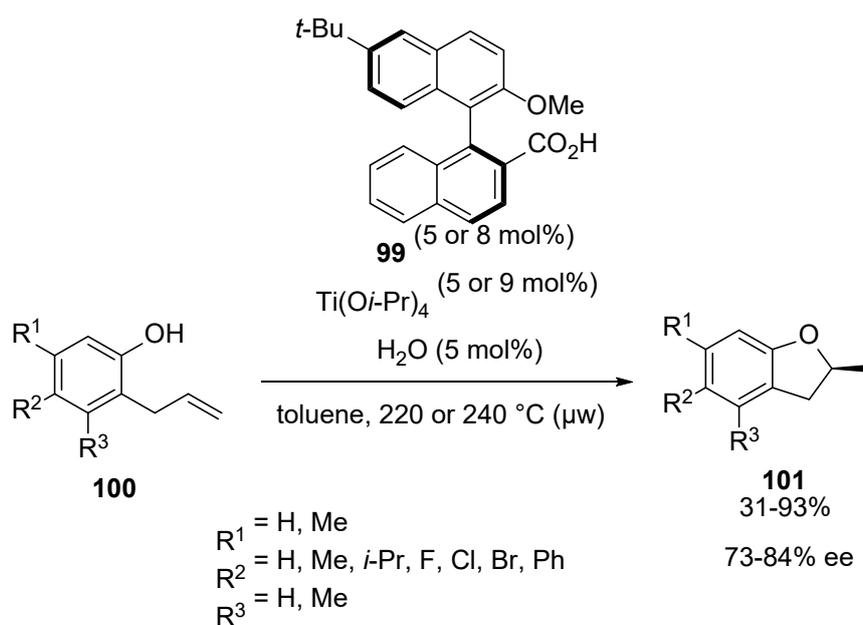
ketones **21** with catecholborane as the reducing agent performed at -20 °C in THF as solvent led to the corresponding secondary alcohols **98** in both moderate to high yields (41-82%) and enantioselectivities (51-98% ee), as shown in Scheme 46. Excellent enantioselectivities of 90-98% ee were obtained for aromatic ketones bearing an electron-withdrawing group on the aromatic ring while lower enantioselectivities (56-86% ee) were obtained in the presence of electron-donating substituents. Lower enantioselectivities (69% ee and 51% ee, respectively) were also observed in the reaction of a conjugated ketone (cyclohexenone) and an heteroaromatic ketone (1-(2-thienyl)ethanone).



**Scheme 46.** Reduction of ketones in the presence of  $\beta$ -dihydroxyamide ligand **97** [104].

The asymmetric hydroalkoxylation of non-activated olefins constitutes a direct route to prepare chiral ethers but is still undeveloped [105]. Among rare chiral metal catalysts capable of promoting these reactions, is a titanium complex derived from binaphthyl carboxylic acid

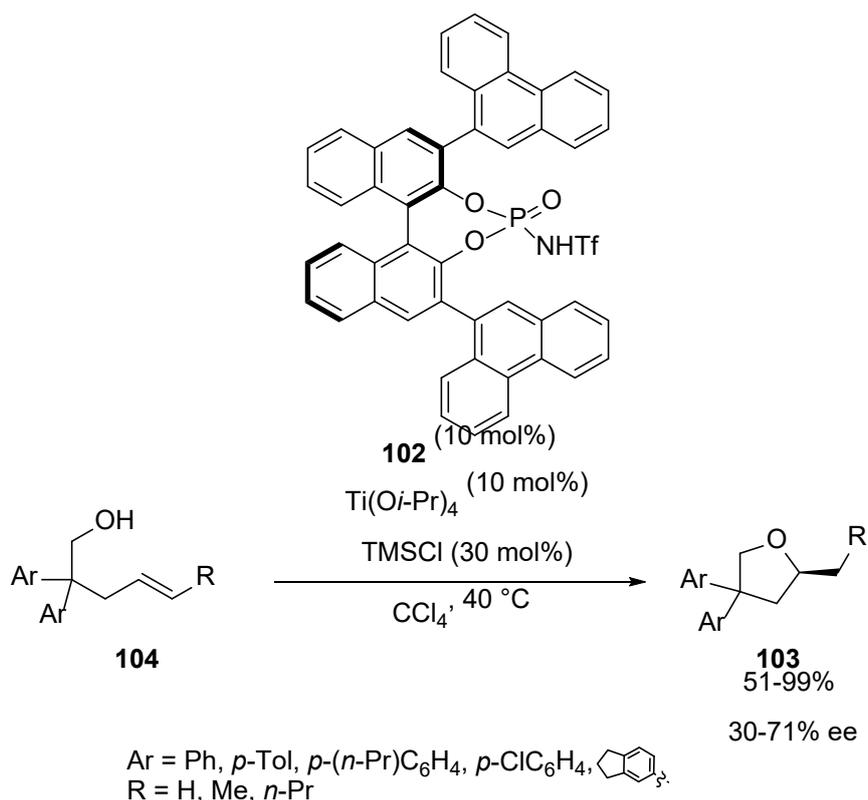
ligand **99** [106]. Indeed, the latter was demonstrated by Hintermann et al. to efficiently catalyze enantioselective intramolecular addition of phenols of non-activated alkenes **100** to give access to the corresponding chiral 2-methylcoumarans **101**. The process was performed at high temperature (220 or 240 °C) under microwave irradiation in toluene as solvent in the presence of a chiral titanium catalyst in situ generated from 5 or 8 mol% of binaphthyl carboxylic acid ligand **99** and 5 or 9 mol% of Ti(O*i*-Pr)<sub>4</sub>. Various 2-allylphenols were tolerated with alkyl, phenyl or halogen groups on the phenyl ring, providing the corresponding chiral cyclic products **101** with low to high yields (31-93%) and good enantioselectivities (73-84% ee), as presented in Scheme 47.



**Scheme 47.** Intramolecular hydroalkoxylation of non-activated alkenes in the presence of binaphthyl carboxylic acid ligand **99** [106].

Related reactions were also investigated in 2020 by Zhao and Zhao by using a chiral titanium catalyst in situ generated from Ti(O*i*-Pr)<sub>4</sub> (10 mol%) and chiral phosphoramidate ligand **102** (10 mol%) [107]. As shown in Scheme 48, a series of chiral tetrahydrofurans **103**

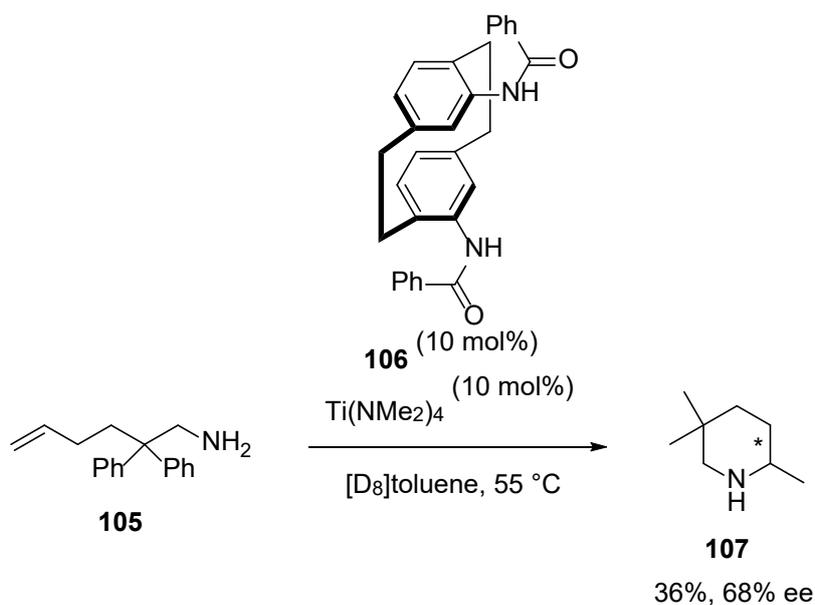
were synthesized through asymmetric intramolecular hydroalkoxylation of the corresponding non-activated alkenes **104** performed at 40 °C in CCl<sub>4</sub> as the solvent in the presence of this catalyst system. These products were obtained in good to quantitative yields (51-99%) and moderate enantioselectivities (30-71% ee).



**Scheme 48.** Intramolecular hydroalkoxylation of non-activated alkenes in the presence of phosphoramidate ligand **102** [107].

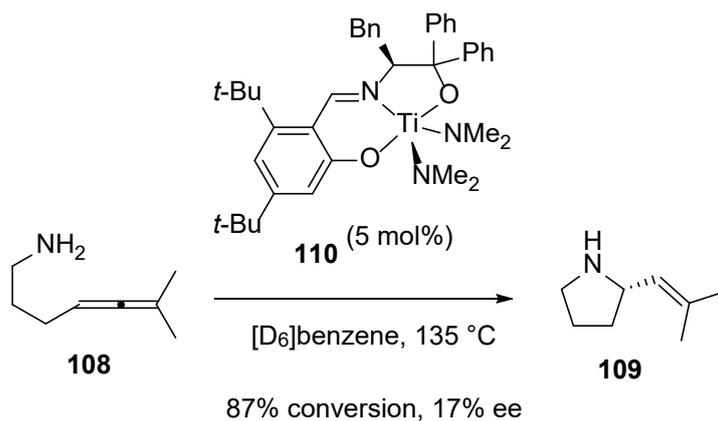
In the same area, chiral amines are directly generated from asymmetric hydroamination of alkenes [2d,108]. In particular, intramolecular versions led to chiral nitrogen heterocycles, such as piperidines or pyrrolidines, which constitute key building blocks in the synthesis of a range of biologically important products [109]. Among chiral metal catalysts employed in these reactions, are titanium chiral complexes [110]. In an example reported in 2017, a promising enantioselectivity (68% ee) was disclosed by Bräse and Schafer in the

intramolecular hydroamination of aminoalkene **105** performed in the presence of a titanium catalyst derived from 10 mol% of novel [2.2]paracyclophanyl bisamide ligand **106** and the same quantity of  $\text{Ti}(\text{NMe}_2)_4$  [111]. This type of ligands combined the planar chirality of the [2.2]paracyclophane skeleton with tethered *N,O*-chelating bisamide ligands. The reaction formed at 55 °C chiral piperidine **107** in 36% yield and 68% ee (Scheme 49).



**Scheme 49.** Intramolecular hydroamination of an aminoalkene in the presence of [2.2]paracyclophanyl bisamide ligand **106** [111].

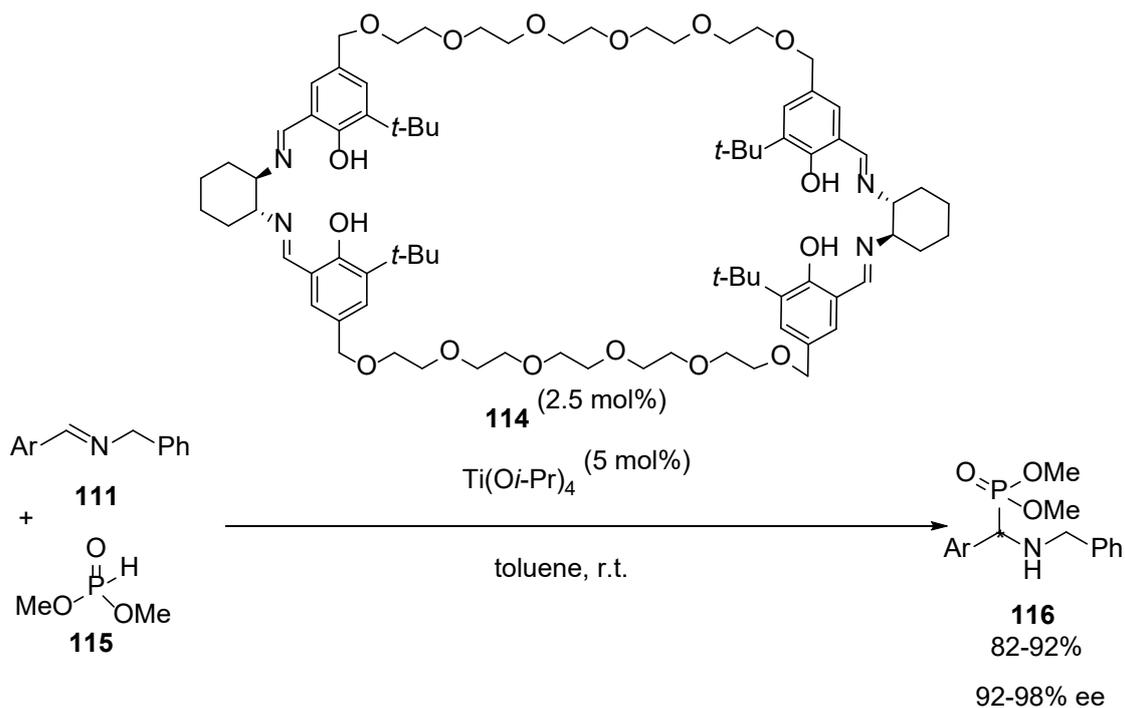
Later in 2019, Johnson et al. reported the synthesis of novel bis-dimethylamide titanium complexes derived from tridentate iminophenol ligands and  $\text{Ti}(\text{NMe}_2)_4$  to be further investigated in asymmetric intramolecular hydroamination of aminoallene **108** into chiral pyrrolidine **109** (Scheme 50) [112]. Complex **110** was found as optimal preformed catalyst, providing at 135 °C and 5 mol% of catalyst loading, chiral cyclic product **109** in high yield (87%) albeit combined with a low enantioselectivity (17% ee).



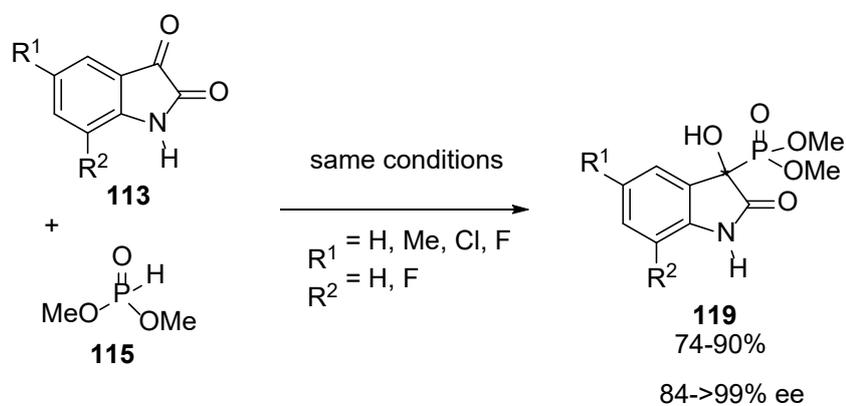
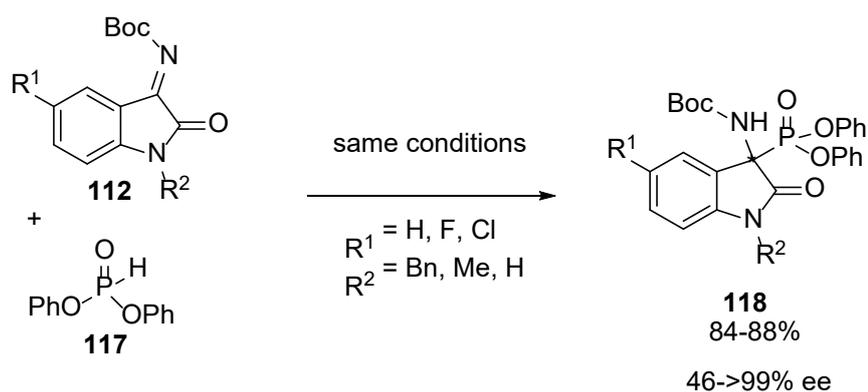
**Scheme 50.** Intramolecular hydroamination of an aminoallene in the presence of Schiff base catalyst **110** [112].

In enantioselective hydrophosphonylation, a dialkyl phosphite is added in the presence of a chiral catalyst to a carbonyl or imine compound to give the corresponding chiral  $\alpha$ -hydroxy/amino phosphonates, constituting synthetic intermediates in the synthesis of many drugs [113]. However, it must be recognized that only few highly enantioselective catalysts to promote these reactions have been reported so far [114]. In 2016, a rare example was disclosed by Khan et al. dealing with asymmetric hydrophosphonylations of various electrophiles spanning from *N*-benzylimines **111** to less reactive isatin imines **112** and isatins **113** performed in the presence of macrocyclic salen titanium catalyst [115]. This novel catalyst was in situ generated at room temperature from 5 mol% of  $\text{Ti}(\text{O}i\text{-Pr})_4$  and 2.5 mol% of macrocyclic ligand **114** in toluene as solvent. Adding dimethylphosphite **115** to a range of *N*-benzylimines **111** in the presence of this catalyst led to the formation of chiral phosphonylated products **116** in uniformly high yields (82-92%) and excellent enantioselectivities (92-98% ee), as illustrated in Scheme 51. In a second time, the authors developed under the same reaction conditions the asymmetric hydrophosphonylation of less reactive isatin-derived ketimines **112** with diphenylphosphite **117** which afforded the corresponding phosphonylated chiral isatin derivatives **118** in high yields (84-88%) and

moderate to excellent enantioselectivities (46->99% ee). The best enantioselectivities (98->99% ee) were achieved in the reaction of substrates without substituent or exhibiting a methyl group on their phenyl ring. On the other hand, ketimines bearing a fluoride or a chloride group on the phenyl ring provided lower enantioselectivities (63-68% ee). An even lower enantioselectivity (46% ee) was obtained in the reaction of an *N*-unprotected isatin derivative ( $R^2 = H$ ). The scope of the reaction could also be successfully extended to variously substituted isatins **113** which led by reaction with dimethylphosphite **115** to the formation of phosphonylated chiral isatins **119** in high yields (74-90%) and homogeneous excellent enantioselectivities (84->99% ee), as shown in Scheme 51. It must be noted that the catalyst could be recycled five times without loss of activity and enantioselectivity. Moreover, the formed isatin derivatives represented potent biologically active products.



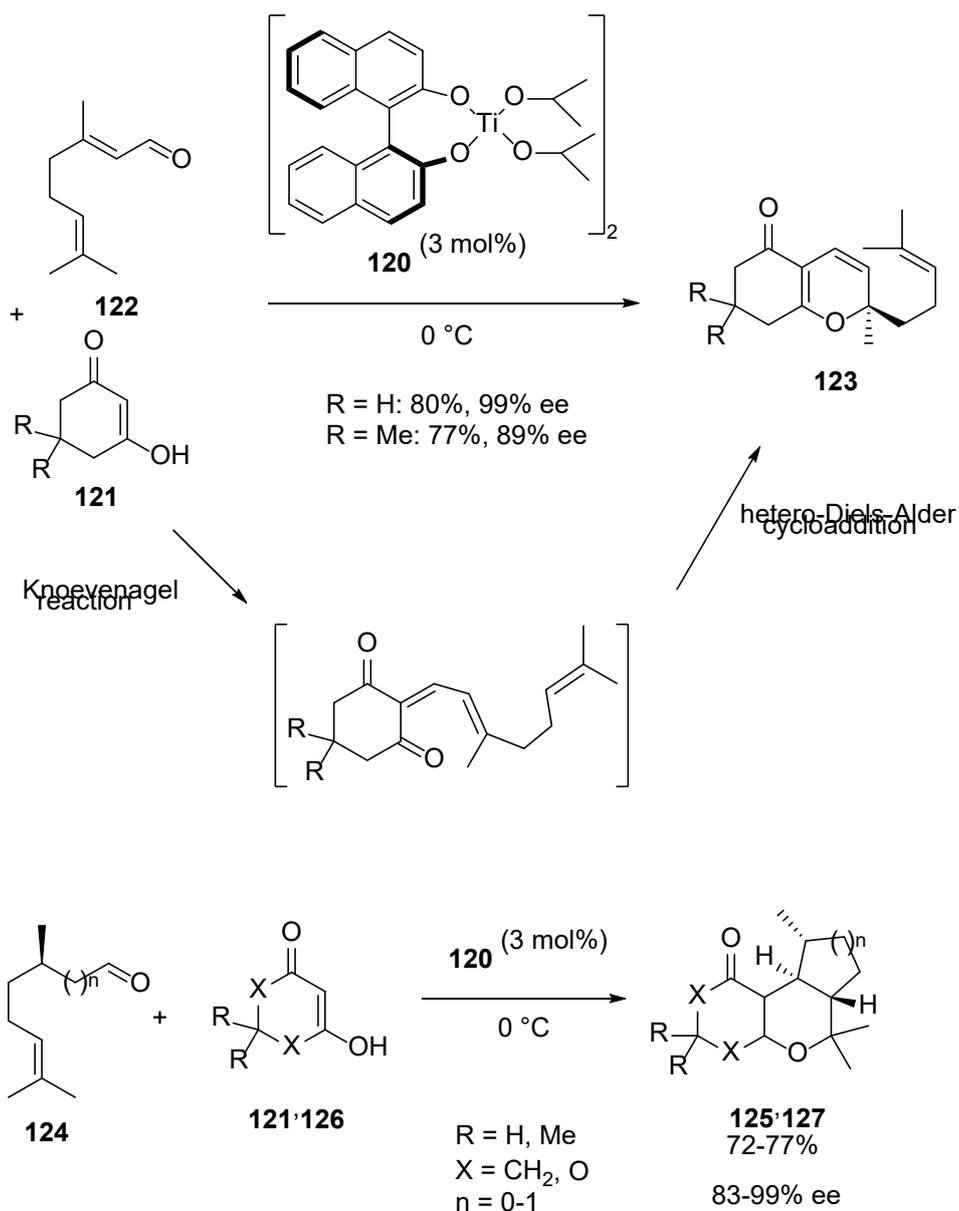
Ar = Ph, *o*-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, *p*-Tol, *p*-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, *o*-FC<sub>6</sub>H<sub>4</sub>, *p*-FC<sub>6</sub>H<sub>4</sub>, *m*-MeOC<sub>6</sub>H<sub>4</sub>, *p*-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>



**Scheme 51.** Hydrophosphonylations of *N*-benzylimines, isatin imines and isatins in the presence of macrocyclic salen catalyst **114** [115].

## 6. Enantioselective titanium-catalyzed domino reactions

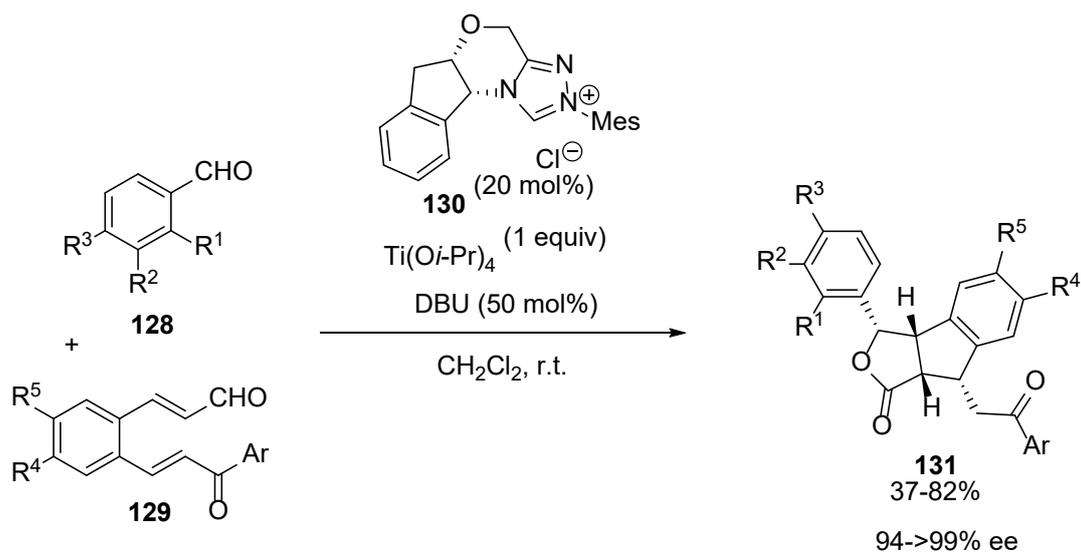
Surprisingly, in spite of the remarkable development of asymmetric catalytic domino reactions [116], this is only recently that the first enantioselective titanium-catalyzed domino reactions have been disclosed. These economic one-step reactions that avoid the isolation and purification of intermediates and costly protection-deprotection processes, have already allowed many highly complex chiral important products to be simply synthesized. For example, a synthesis of chiral bicyclic tetrahydro-2*H*-chromen-5(6*H*)-one and tricyclic octahydro-2*H*-benzo[*c*]-chromen-1(6*H*)-one derivatives was achieved in 2015 by Bhat et al. on the basis of enantioselective titanium-catalyzed domino Knoevenagel/hetero-Diels–Alder cycloaddition reactions of cyclic 1,3-dicarbonyl compounds with aldehydes [117]. Remarkably, the processes could be performed under solvent-free conditions in the presence of only 3 mol% of dinuclear titanium-isopropoxy-(*S*)-BINOLate catalyst **120**. The reaction of cyclic 1,3-dicarbonyl compounds **121**, such as 1,3-cyclohexadienone (R = H) and dimedone (R = Me), with an  $\alpha,\beta$ -unsaturated aldehyde, such as citral **122**, led at 0 °C to the corresponding chiral bicyclic tetrahydro-2*H*-chromen-5(6*H*)-one derivatives **123** with both excellent yields (77-80%) and enantioselectivities (89-99% ee), as illustrated in Scheme 52. The same cyclic 1,3-dicarbonyl substrates **121** also reacted with saturated aldehydes **124**, such as (*R*)-citronellal (n = 1) and (*R*)-melonal (n = 0), to give the corresponding chiral tricyclic octahydro-2*H*-benzo[*c*]-chromen-1(6*H*)-one derivatives **125** (Scheme 52) in excellent yields (76-77%) and enantioselectivities (88-99% ee). These economic reaction conditions were also successfully applied to Meldrum's acid **126** (X = O, R = Me, n = 1) which underwent the domino reaction with (*R*)-citronellal to afford the corresponding tricyclic product **127** in 72% yield and 83% ee.



**Scheme 52.** Domino Knoevenagel/hetero-Diels–Alder cycloaddition reactions of cyclic 1,3-dicarbonyl compounds with aldehydes in the presence of dinuclear titanium-isopropoxy-(*S*)-BINOLate catalyst **120** [117].

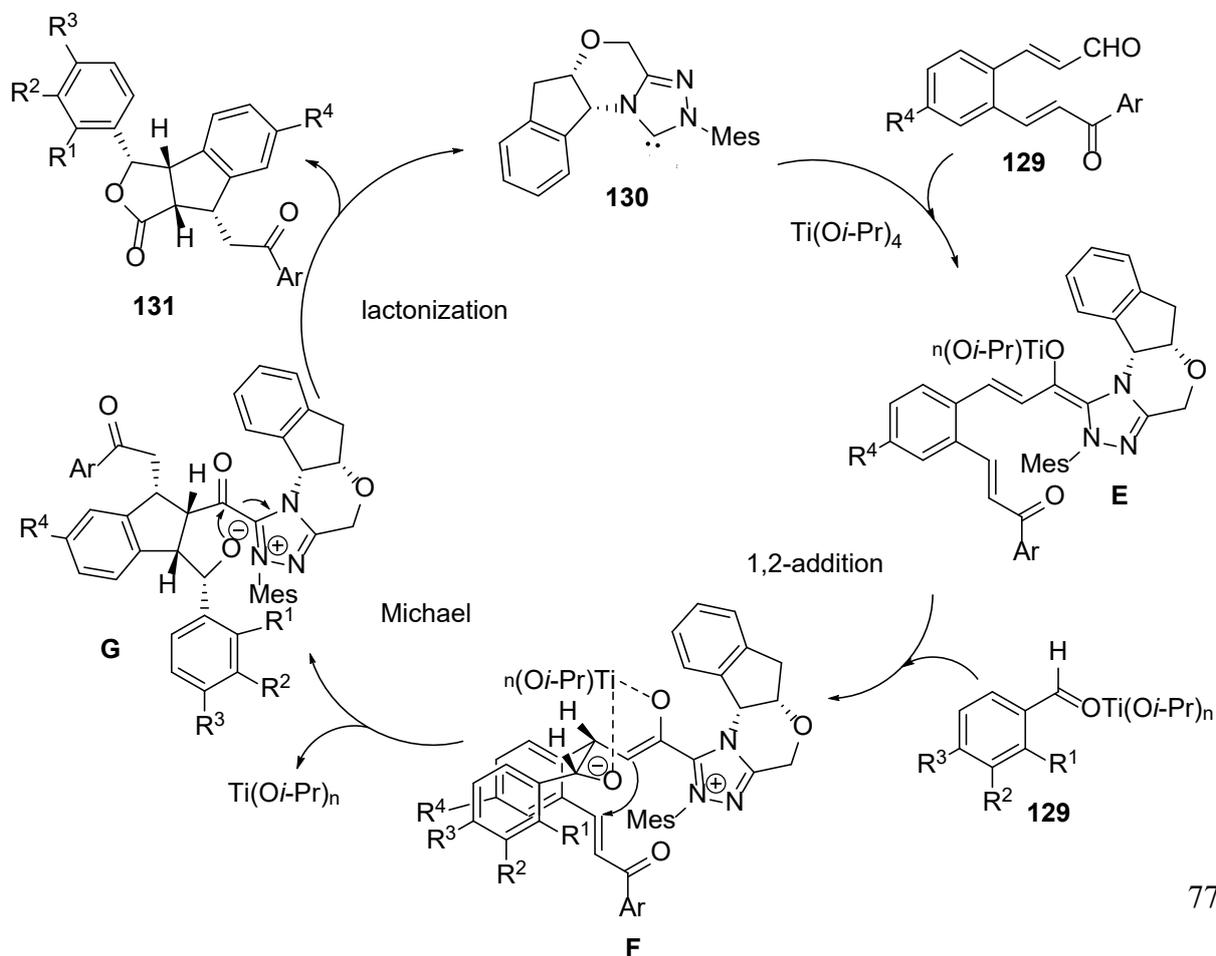
Indane-fused butyrolactones constitute the skeleton of many biologically important products [118]. In 2016, a novel and rare asymmetric route to this type of products was reported by Cheng et al. on the basis of an enantioselective titanium-catalyzed domino reaction occurring

between aldehydes **128** and 2-arylvinylcinnamaldehydes **129** [119]. Actually, the process involved a cooperative dual catalysis with one equivalent of  $\text{Ti}(\text{O}i\text{-Pr})_4$  and 20 mol% of chiral N-heterocyclic carbene catalyst **130**. As depicted in Scheme 53, the latter added to 2-arylvinylcinnamaldehyde **129** to give dienamine intermediate **E** which subsequently underwent an intermolecular nucleophilic 1,2-addition to the carbonyl group of aldehyde **129** activated by  $\text{Ti}(\text{O}i\text{-Pr})_4$ , leading to intermediate **F**. Then, an intramolecular Michael addition of enolate to the enone species of **F** afforded indane intermediate **G**, which further underwent a final lactonization to yield chiral tetrahydroindeno[1,2-*c*]furan-1-one **131**. A range of products **131** were generated at room temperature in dichloromethane as solvent through this domino 1,2-addition/Michael/lactonization reaction with moderate to high yields (37-82%) and homogeneously excellent enantioselectivities (94->99% ee). Remarkably, the catalyst system tolerated *o*-alkynyl, *o*-alkenyl, as well as aromatic benzaldehydes **128**, exhibiting either electron-withdrawing or electron-donating substituents on the phenyl ring. Moreover, variously substituted 2-arylvinylcinnamaldehydes **129** were compatible.



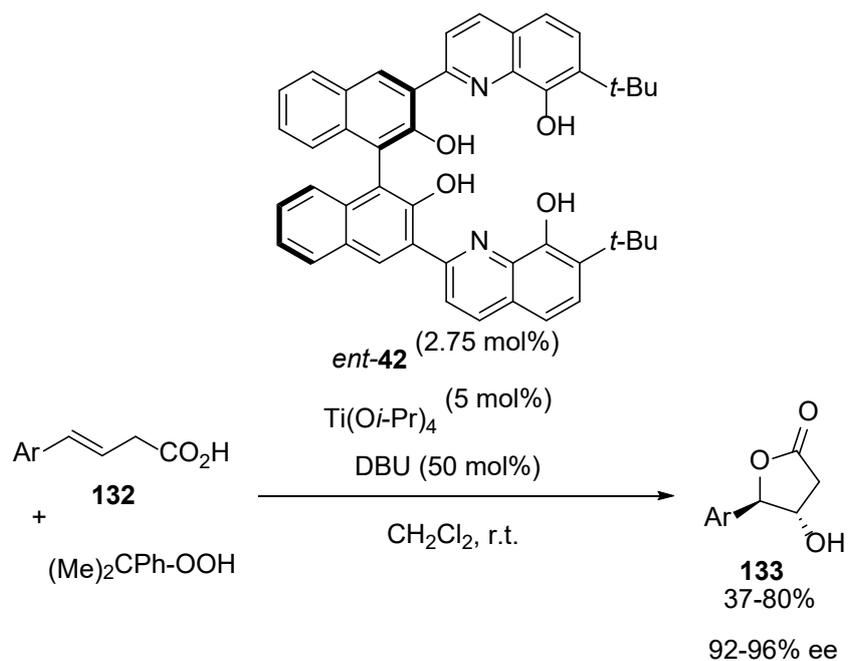
$\text{R}^1 = \text{PhC}\equiv\text{C}$ ,  $p\text{-FC}_6\text{H}_4\text{C}\equiv\text{C}$ ,  $p\text{-TolC}\equiv\text{C}$ ,  $p\text{-MeOC}_6\text{H}_4\text{C}\equiv\text{C}$ , (*E*)- $\text{PhCH}=\text{CH}$ , Et, OMe, Br,  $\text{CF}_3$   
 $\text{R}^2 = \text{H}$ , OMe, Br,  $\text{CF}_3$   
 $\text{R}^3 = \text{H}$ , F, Me, OMe,  $\text{CF}_3$   
 $\text{R}^4 = \text{H}$ , Me, OMe, F  
 $\text{R}^5 = \text{H}$ , F, Me, OMe  
 Ar = Ph,  $p\text{-BrC}_6\text{H}_4$ ,  $p\text{-Tol}$ ,  $p\text{-MeOC}_6\text{H}_4$

mechanism:

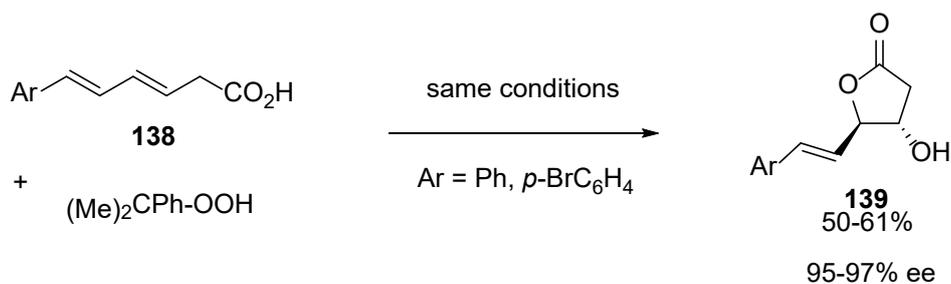
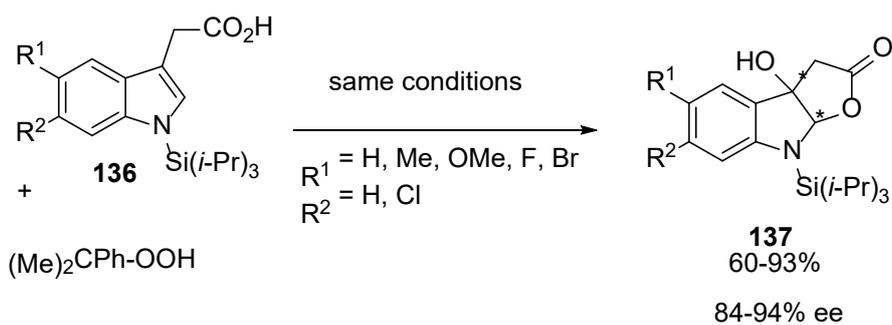
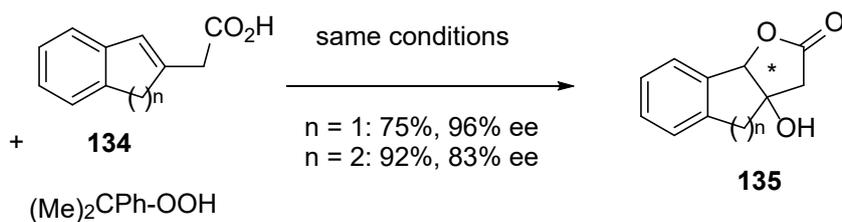


**Scheme 53.** Domino 1,2-addition/Michael/lactonization reaction of 2-arylvinylcinnamaldehydes with aldehydes in the presence of N-heterocyclic carbene catalyst **130** [119].

Another type of domino reaction was developed by Sawano and Yamamoto in 2019 on the basis of asymmetric titanium catalysis [120]. It concerned an enantioselective domino epoxidation/cyclization reaction between  $\beta,\gamma$ -unsaturated carboxylic acids **132** and cumene hydroperoxide as oxidant, providing chiral  $\gamma$ -lactones **133** as single diastereomers. It occurred at room temperature in dichloromethane as the solvent in the presence of a catalyst system composed of 5 mol% of  $\text{Ti}(\text{O}i\text{-Pr})_4$  and only 2.75 mol% of (*R*)-BINOL-derived tetraol ligand *ent*-**42**. After epoxidation of the double bond of  $\beta,\gamma$ -unsaturated carboxylic acid **132** with cumene hydroperoxide, the formed intermediate epoxide was submitted to ring-opening through intramolecular attack of the carboxylic acid in the presence of DBU as base to give the final cyclic product. As illustrated in Scheme 54, a variety of  $\beta,\gamma$ -unsaturated carboxylic acids **132** bearing an (hetero)aromatic group (R) afforded the corresponding almost enantiopure  $\gamma$ -lactones **133** (92-96% ee) with moderate to good yields (37-80%). In addition to these disubstituted olefins, trisubstituted alkenes **134** were also tolerated, leading to products **135** in both high yields (75-92%) and enantioselectivities (83-96% ee). Furthermore, more complex *N*-triisopropylsilylated indole 3-acetic acid derivatives **136** reacted smoothly to provide chiral tricyclic products **137** in high enantioselectivities (84-94% ee) and good yields (60-93%), as shown in Scheme 54. The authors also investigated the reaction of  $\beta,\gamma,\delta,\varepsilon$ -unsaturated carboxylic acids **138** bearing a conjugated double bond. A total regioselectivity was observed since only almost enantiopure (95-97% ee) products **139** were generated in good yields (50-61%) with no epoxidation of the other double bond (Scheme 54).

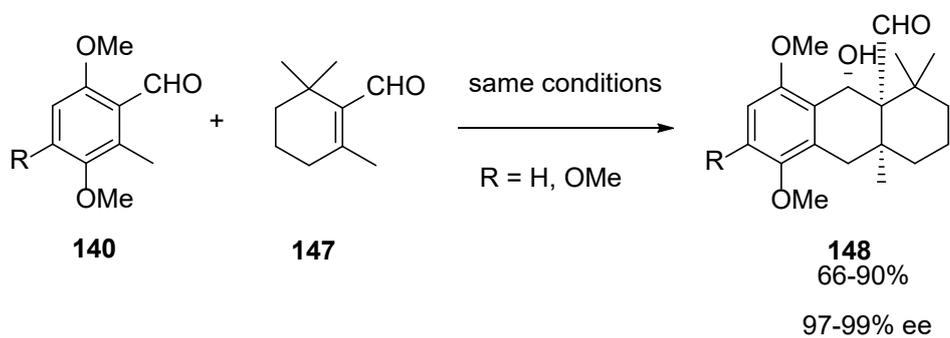
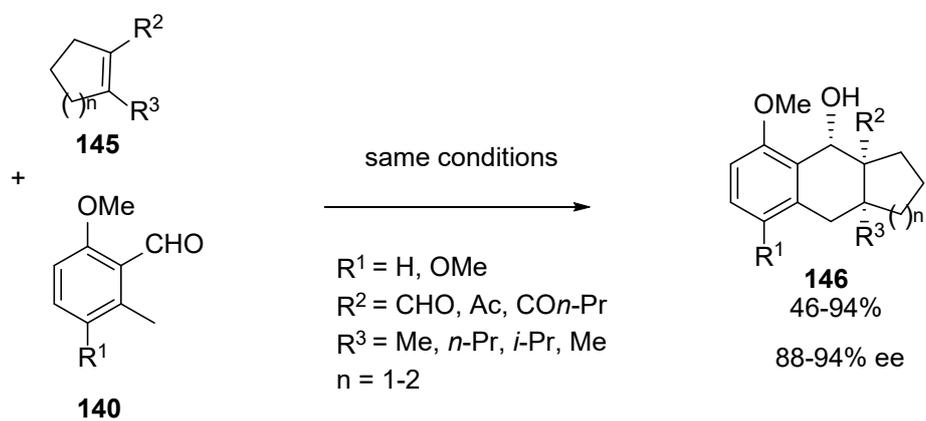
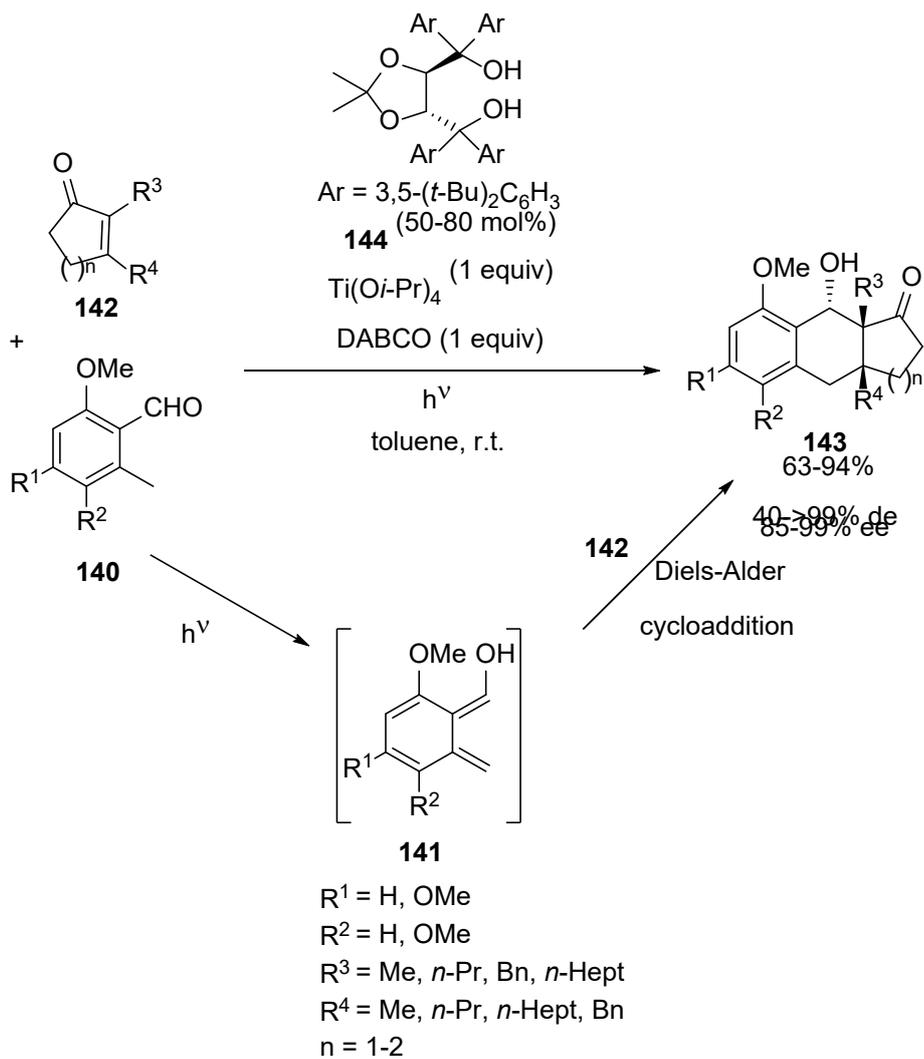


Ar = Ph, *p*-Tol, *p*-MeOC<sub>6</sub>H<sub>4</sub>, *p*-FC<sub>6</sub>H<sub>4</sub>, *p*-ClC<sub>6</sub>H<sub>4</sub>,  
*p*-BrC<sub>6</sub>H<sub>4</sub>, *m*-Tol, *o*-Tol, 2-Naph, 2-furyl, 2-thienyl



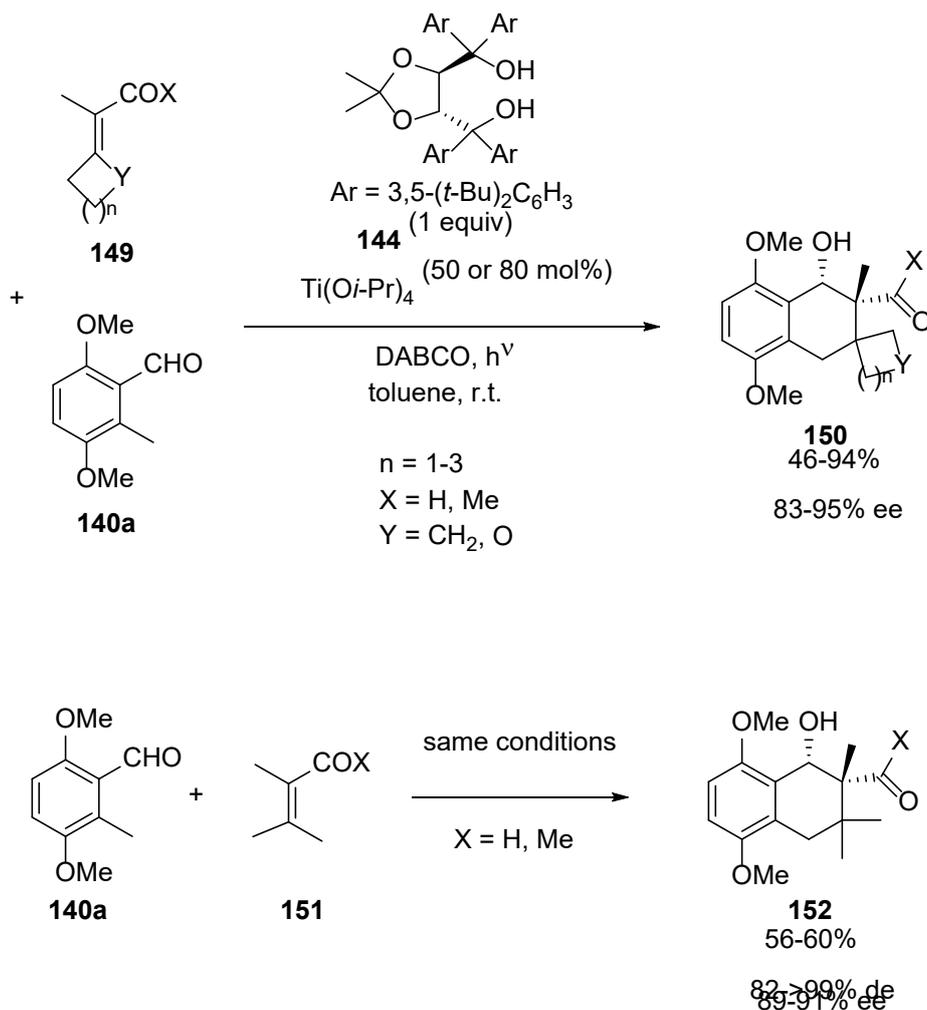
**Scheme 54.** Domino epoxidation/cyclization reactions of  $\beta,\gamma$ -unsaturated carboxylic acids in the presence of (*R*)-BINOL-derived ligand *ent*-**42** [120].

In 2021, Gao et al. described enantioselective domino photoenolization/Diels–Alder reactions of benzaldehydes with sterically hindered dienophiles [121]. As presented in Scheme 55, the UV light-induced enolization of electron-rich 2-methylbenzaldehydes **140** generated a highly active diene hydroxy-*o*-quinodimethane **141** via an excited-state species, which was then trapped by a dienophile, such as cyclic enones **142**, through Diels–Alder cycloaddition to form the corresponding chiral cycloadducts **143**. The process was performed at room temperature in toluene as the solvent in the presence of one equivalent of  $\text{Ti}(\text{O}i\text{-Pr})_4$  as precatalyst combined with 50-80 mol% of chiral TADDOL ligand **144**. Under these conditions, a series of tetrasubstituted cyclopentenones and cyclohexenones reacted with differently substituted 2-methylbenzaldehydes to give the desired tricyclic chiral products **143** with good to high yields (63-94%) and uniformly high enantioselectivities (85-99% ee). The scope of the domino reaction was extended to other sterically hindered cyclic dienophiles, such as tetrasubstituted cyclopentenones and cyclohexenones **145**, which led by reaction with 2-methylbenzaldehydes **140**, the corresponding chiral tricyclic cycloadducts **146** with moderate to high yields (46-94%) and homogeneously very high ee values (88-94% ee). In addition, even betacyclocitral **147** bearing geminal dimethyl groups adjacent to the tetrasubstituted unsaturated aldehyde was compatible with the catalyst system since it provided by reaction with different 2-methylbenzaldehydes **140** the corresponding tricyclic cycloadducts **148** bearing three vicinal all-carbon quaternary centers as single diastereomers in good yields (66-90%) and uniformly excellent enantioselectivities (97-99% ee).



**Scheme 55.** Domino photoenolization/Diels–Alder reactions of 2-methylbenzaldehydes with cyclic tetrasubstituted olefins in the presence of (*R*)-TADDOL-derived ligand **144** [121].

The same catalyst system was also compatible with acyclic tetrasubstituted olefins **149** bearing an *exo*-unsaturated aldehyde (X = H) or acetyl group (X = Me) as dienophiles, as depicted in Scheme 56. Indeed, acyclic tetrasubstituted olefins **149** smoothly reacted with 2-methyl-3,6-dimethoxybenzaldehyde **140a** to afford the corresponding chiral tricyclic products **150** containing a spiro all-carbon quaternary stereocenter with moderate to high yields (46-94%) and high enantioselectivities (83-95% ee) [121]. These spirocyclic molecules ranged from cyclobutane to cyclohexane (n= 1-3) and also included pyran rings (Y = O). Moreover, acyclic tetrasubstituted alkenes **151** were tolerated, leading by reaction with the same benzaldehyde **140a**, to the corresponding bicyclic adducts **152** with both high diastereo- (>99% de) and enantioselectivities (89-91% ee) albeit combined with moderate yields (56-60%) which could be related to the flexibility of the alkenes. It must be noted that this novel simple one-pot methodology constituted the first example of using a direct UV-light-mediated cycloaddition to build chiral adjacent quaternary centers at bridgeheads, which demonstrates its potential in the synthesis of many useful complex chiral polycyclic rings for medicinal chemistry.

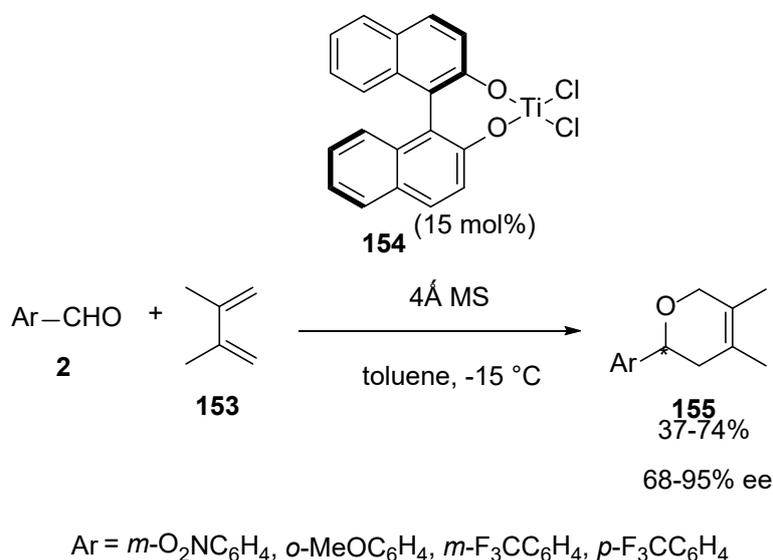


**Scheme 56.** Domino photoenolization/Diels–Alder reactions of 2-methylbenzaldehydes with acyclic olefins in the presence of (*R*)-TADDOL-derived ligand **144** [121].

## 7. Enantioselective titanium-catalyzed cycloaddition reactions

The asymmetric hetero-Diels–Alder cycloaddition allows the direct access to a wide range of chiral six-membered heterocycles, including many building blocks for the synthesis of bioactive and natural products [1a,122]. Especially, the asymmetric hetero-Diels–Alder reaction of activated dienes, such as Danishefsky’s dienes, with aldehydes has been widely developed in the presence of chiral metal catalysts including titanium complexes derived from BINOL derivatives among other ligands [123]. In 2016, Bansal et al. investigated the

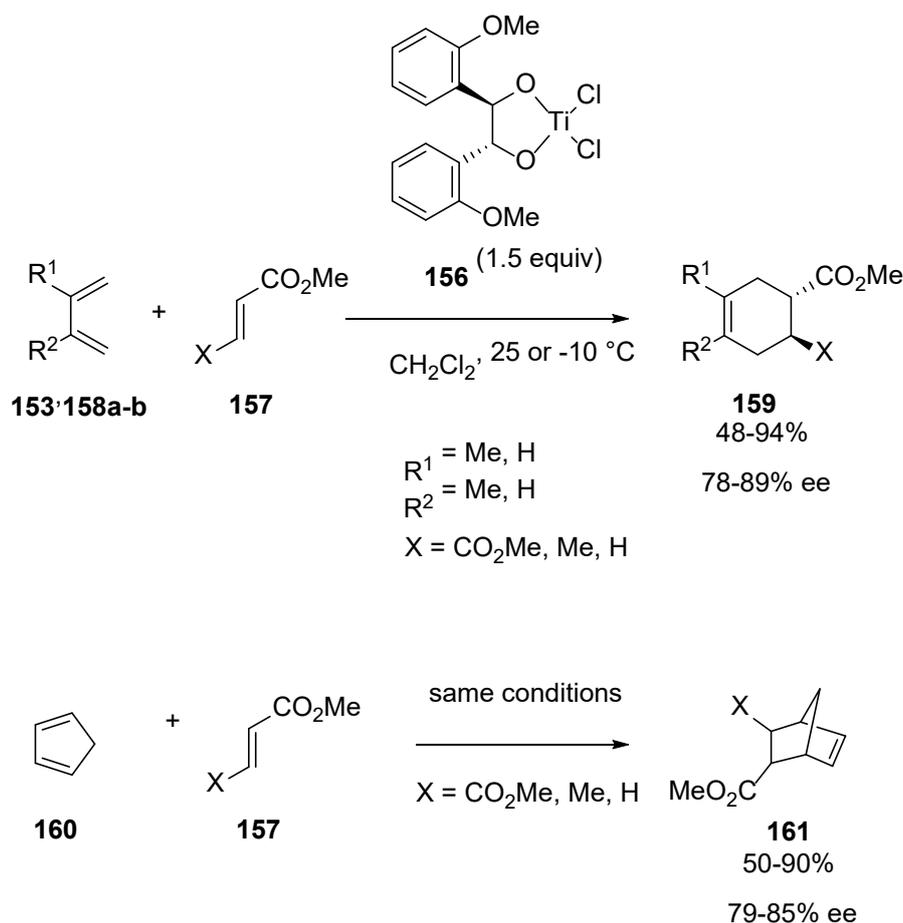
enantioselective oxa-Diels–Alder cycloaddition of non-activated dienes, such as 2,3-dimethylbutadiene **153**, with aromatic aldehydes **2** in the presence of 15 mol% of preformed (*R*)-BINOL-derived titanium dichloride catalyst **154** in toluene as solvent [124]. It led at -15 °C to chiral 3,6-dihydro-2*H*-pyrans **155** in moderate to good yields (37-74%) and good to high enantioselectivities (68-95% ee), as presented in Scheme 57. The best enantioselectivity (95% ee) was reached in the reaction of *o*-methoxybenzaldehyde.



**Scheme 57.** Hetero-Diels–Alder cycloaddition of aromatic aldehydes with 2,3-dimethylbutadiene in the presence of (*R*)-BINOL-derived catalyst **154** [124].

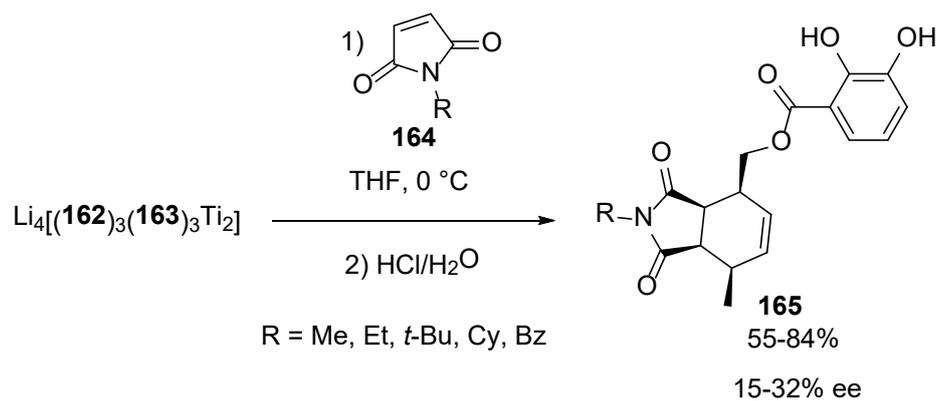
Through the formation of carbon–carbon bonds, the asymmetric Diels–Alder cycloaddition allows a simple route to many useful chiral six-membered products [125]. Various types of chiral titanium catalysts have already been successfully applied to promote such reactions [126]. In a recent example, Patwardhan and Choughule employed novel titanium complex **156** derived from a chiral 1,2-diol to promote the Diels–Alder cycloaddition of carboxylic ester dienophiles **157** with 1,3-dienes (Scheme 58) [127]. In most cases, the reaction was

performed at 25 °C in dichloromethane as the solvent in the presence of 1.5 equivalent of preformed catalyst **156**. In the reaction of  $\alpha,\beta$ -unsaturated carboxylic ester **157** with acyclic 1,3-dienes, such as 2,3-dimethylbutadiene **153**, 2-methylbutadiene **158a** or butadiene **158b**, the corresponding chiral cyclohexene products **159** were formed in homogeneously high enantioselectivities (78-89% ee) combined with moderate to excellent yields (48-94%). Comparable results (79-85% ee, 50-90% yields) were achieved in the reaction of  $\alpha,\beta$ -unsaturated carboxylic ester **157** with cyclopentadiene **160**, leading to product **161** (Scheme 58).

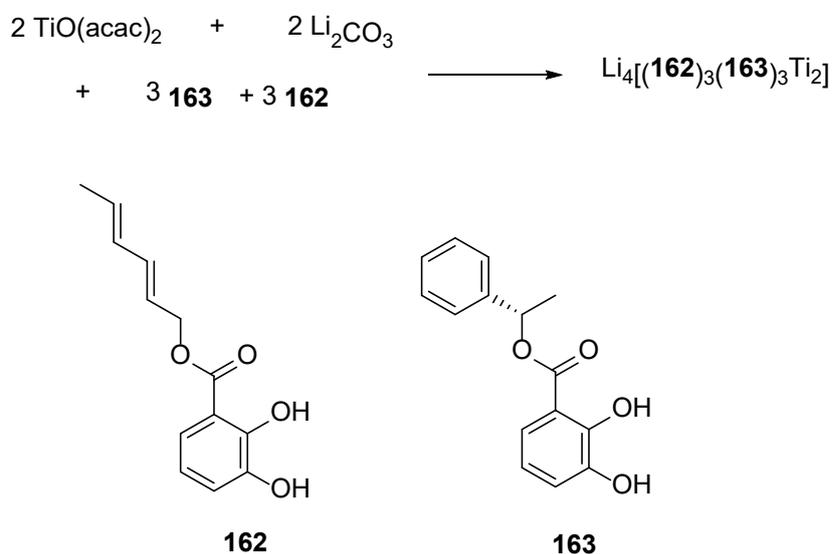


**Scheme 58.** Diels–Alder cycloadditions of carboxylic ester dienophiles with 1,3-dienes in the presence of 1,2-diol-derived catalyst **156** [127].

On the other hand, many asymmetric Diels–Alder reactions are based on the use of chiral auxiliaries [128]. In this context, Albrecht et al. introduced in 2016 a novel supramolecular concept for the auxiliary control of the Diels–Alder cycloaddition of maleimides with a 1,3-diene [129]. A dimeric titanium helicate catalyst  $\text{Li}_4[(\mathbf{162})_3(\mathbf{163})_3\text{Ti}_2]$ , incorporating chiral ligands **161** and achiral 1,3-diene-substituted ligands **162**, was synthesized from  $\text{TiO}(\text{acac})_2$ ,  $\text{Li}_2\text{CO}_3$  and 3 equivalents of each ligand **162** and **163**. The latter reacted at 0 °C with dienophiles, such as *N*-alkylmaleimides **164**, in THF as solvent to afford after hydrolysis the corresponding chiral cycloadducts **165** as single diastereomers in good yields (55-84%) and low enantioselectivities (15-32% ee) along with recovered chiral ligand **163** (Scheme 59).



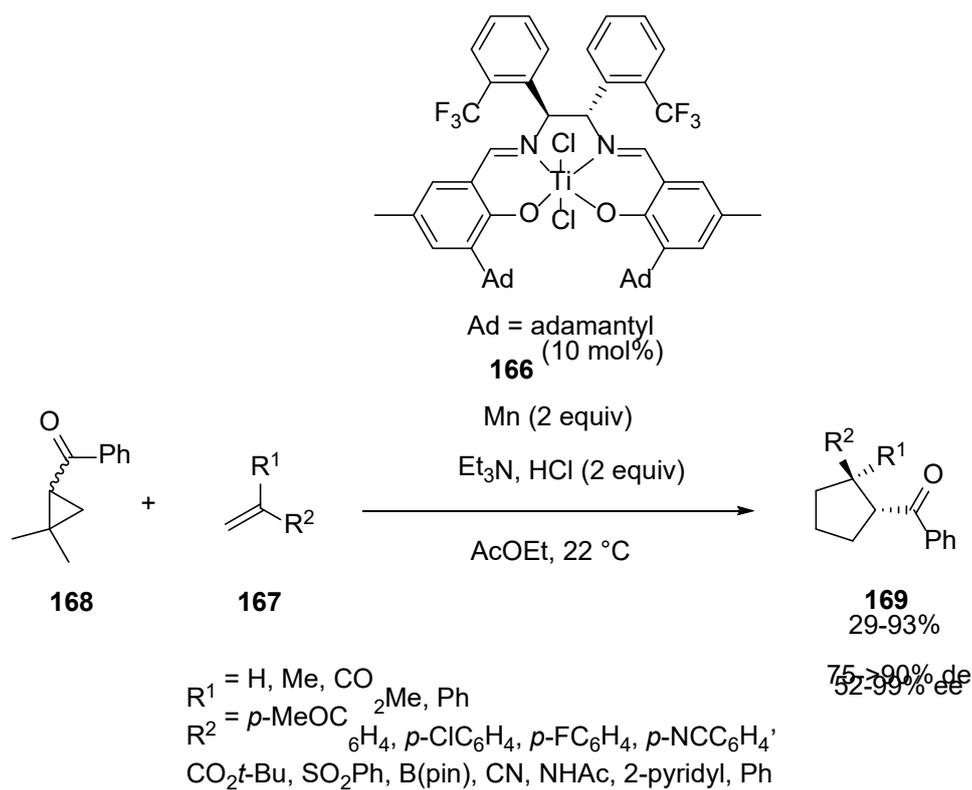
preparation of  $\text{Li}_4[(\mathbf{162})_3(\mathbf{163})_3\text{Ti}_2]$ :



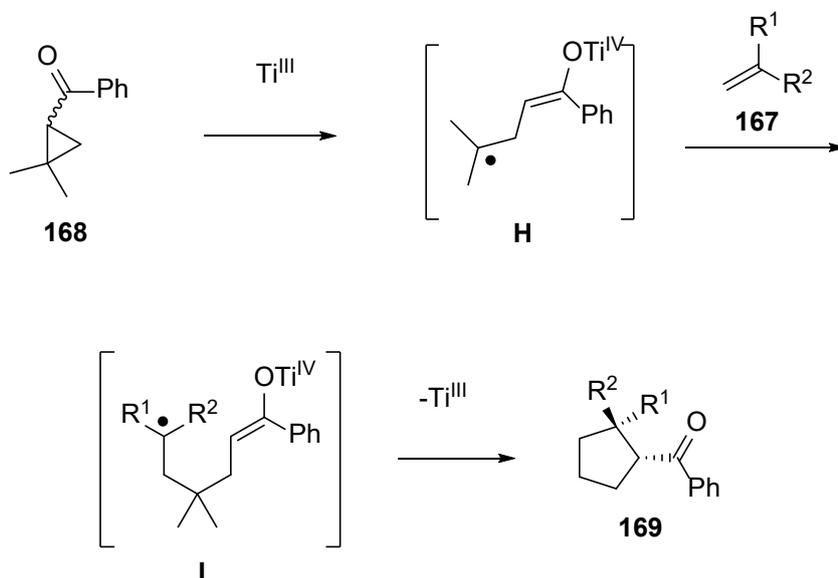
**Scheme 59.** Diels–Alder cycloaddition of maleimides with 1,3-dienes in the presence of dimeric titanium catalyst  $\text{Li}_4[(\mathbf{162})_3(\mathbf{163})_3\text{Ti}_2]$  [129].

In 2020, Lin and Sigman reinvestigated enantioselective [3+2] cycloadditions of cyclopropyl ketones with alkenes catalyzed by (salen) titanium complexes [130]. When using 10 mol% of optimal salen titanium complex **166** in ethyl acetate as the solvent, the reaction of a range of alkenes **167** with cyclopropyl ketone **168** performed at 22 °C in the presence of one equivalent of manganese as the reductant led to the corresponding chiral polysubstituted cyclopentanes **169** in variable yields (29-93%), good to high diastereoselectivities (75->90%

de) and moderate to excellent enantioselectivities (52-99% ee), as summarized in Scheme 60. While high enantioselectivities were generally achieved in the reaction of electron-rich alkenes, that of electron-deficient alkenes was less enantioselective. For example, the lowest ee value (52% ee) was obtained in the reaction of acrylonitrile ( $R^1 = H$ ,  $R^2 = CN$ ). The reaction evolved through a single electron mechanism which is depicted in Scheme 60. It involved the generation of an active titanium(III) catalyst via single electron reduction by manganese. Subsequently, reductive ring opening of the cyclopropyl ketone occurred regioselectively under the action of this titanium(III) complex to form tertiary carbon-centered radical **H**. The latter was further added to the alkene to give intermediate **I**, which finally cyclized into chiral cyclopentane **169**.



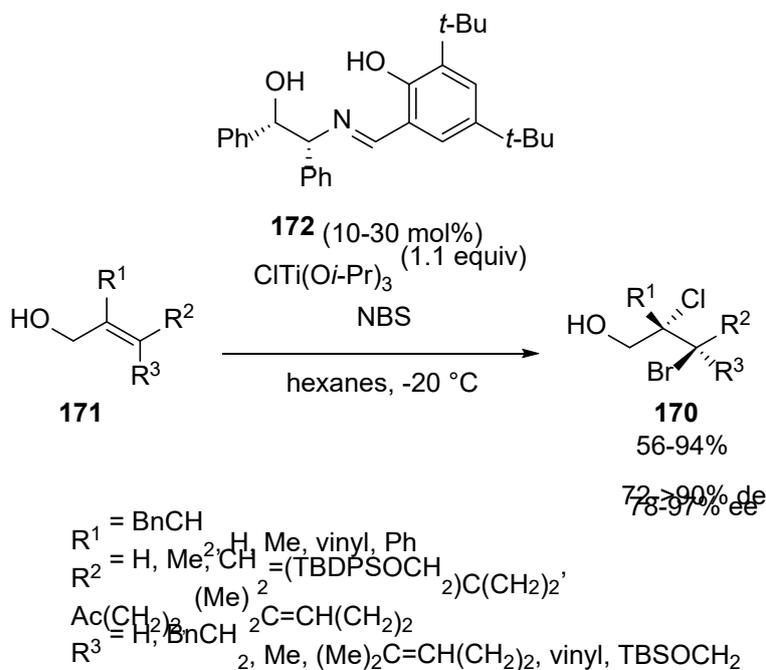
proposed mechanism:



**Scheme 60.** [3+2] Cycloaddition of cyclopropyl ketones with alkenes in the presence of salen titanium catalyst **166** [130].

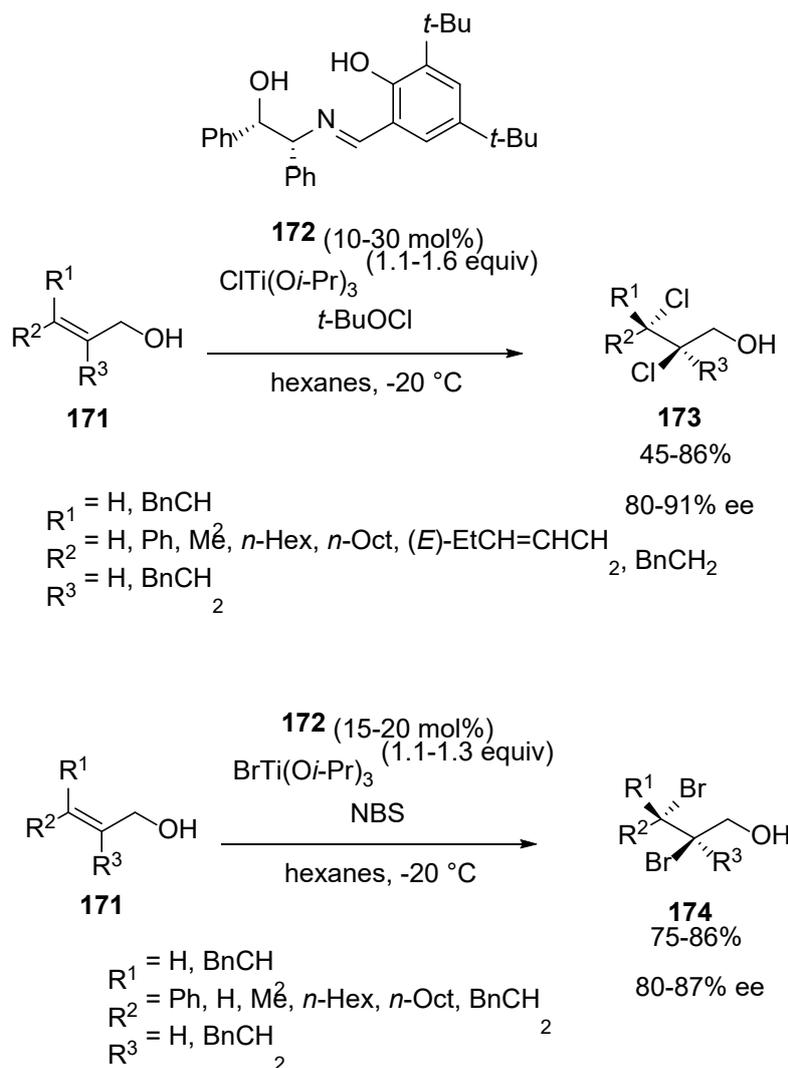
## 8. Enantioselective titanium-catalyzed dihalogenation reactions of alkenes

The rare examples of enantioselective alkene dihalogenation involved addition of two same halogens [131]. In 2015, Burns et al. described for the first time a regio- and enantioselective addition of two different halogens to an alkene [132]. Indeed, a series of bromochlorinated chiral products **170** were synthesized from the reaction of the corresponding allylic alcohols **171** with NBS in the presence of  $\text{ClTi}(\text{O}i\text{-Pr})_3$  combined with chiral Schiff base ligand **172** (Scheme 61). This highly regio-, -diastereo- and enantioselective bromochlorination was performed at  $-20\text{ }^\circ\text{C}$  in hexanes as solvent, yielding products **170** in good yields (56-94%) and both high diastereo- (72->90% de) and enantioselectivities (78-97% ee). 1,1-Disubstituted, trisubstituted and *cis*-disubstituted alkenes all reacted with high levels of regio- and stereoselectivities while *trans*-disubstituted allylic alcohols provided much lower regioselectivity. Moreover, the substrates could bear a supplementary double bond or functionalities, such as ketone and silyl ether groups.



**Scheme 61.** Bromochlorination of allylic alcohols in the presence of Schiff base ligand **172** [132127].

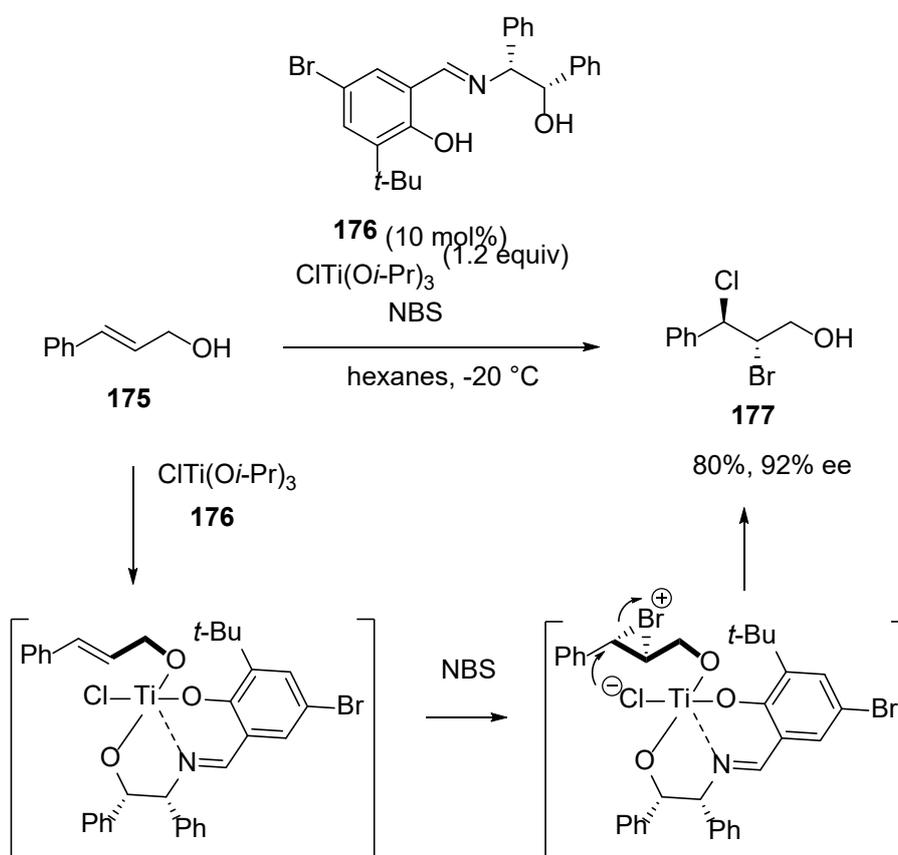
The same catalyst system was also applied by these authors to the enantioselective dichlorination of allylic alcohols **171** by using *tert*-butylhypochlorite as a selective source of electrophilic chlorine [133]. As shown in Scheme 62, a range of chiral dichlorinated products **173** were synthesized at -20 °C in hexanes as solvent with high enantioselectivities (80-91% ee) and good yields (45-86%) starting from the corresponding 1,1-disubstituted and *trans*- and *cis*-disubstituted allylic alcohols **171**. This methodology allowed a novel entry to polychlorinated natural products, such as chlorosulfolipids. Indeed, this asymmetric dichlorination was used as first step in the total synthesis of *ent*-(-)-danicalipin A and *ent*-(-)-deschloromytilipin A. In a second time, the authors investigated the corresponding dibromination reaction of allylic alcohols in the presence of the same Schiff base ligand **172** in hexanes at -20 °C. Bromination agents, such as NBS and BrTi(*Oi*-Pr)<sub>3</sub>, were used in place of *t*-BuOCl and ClTi(*Oi*-Pr)<sub>3</sub>. Under these conditions, the dibromination of *trans*- and *cis*-disubstituted as well as 1,1-disubstituted allylic alcohols **171** yielded the corresponding chiral dibrominated products **174** in both high yields (75-86%) and enantioselectivities (80-87% ee), as illustrated in Scheme 62.



**Scheme 62.** Dichlorination/dibromination of allylic alcohols in the presence of Schiff base ligand **172** [133127].

In 2016, Yang and Xu developed the first asymmetric bromochlorination of cinnamyl alcohol **175** (Scheme 63) since this type of aromatic substrates were not included in the early work described by Burns and co-workers (Scheme 62) [134]. Among a wide range of designed chiral Schiff base ligands investigated in this reaction, multifunctional ligand **176** was found optimal under reaction conditions similar to those employed in Burns's enantioselective bromochlorination. Indeed, the reaction of cinnamyl alcohol **175** with NBS and  $\text{ClTi}(\text{O}i\text{-Pr})_3$  in the presence of 10 mol% of ligand **176** afforded with complete

regioselectivity the corresponding aromatic bromochloroalcohol **177** in 80% yield and 92% ee. A mechanism is proposed in Scheme 63 in which the observed regioselectivity is explained by the benzylic nature of the intermediate bromonium species, leading to an inherent electronic preference in the substrate which favored a chloride attack at the benzylic position.

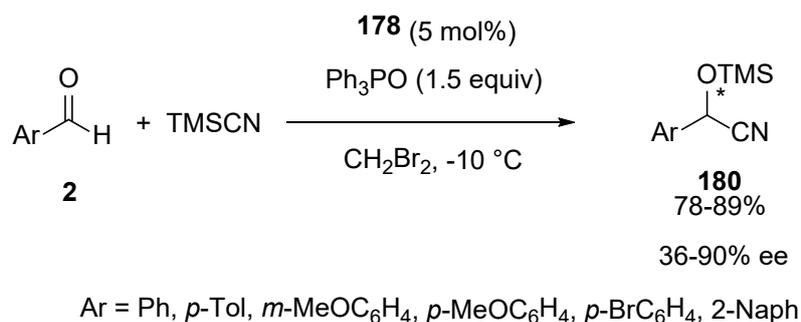


**Scheme 63.** Bromochlorination of cinnamyl alcohol in the presence of Schiff base ligand **176** [134127].

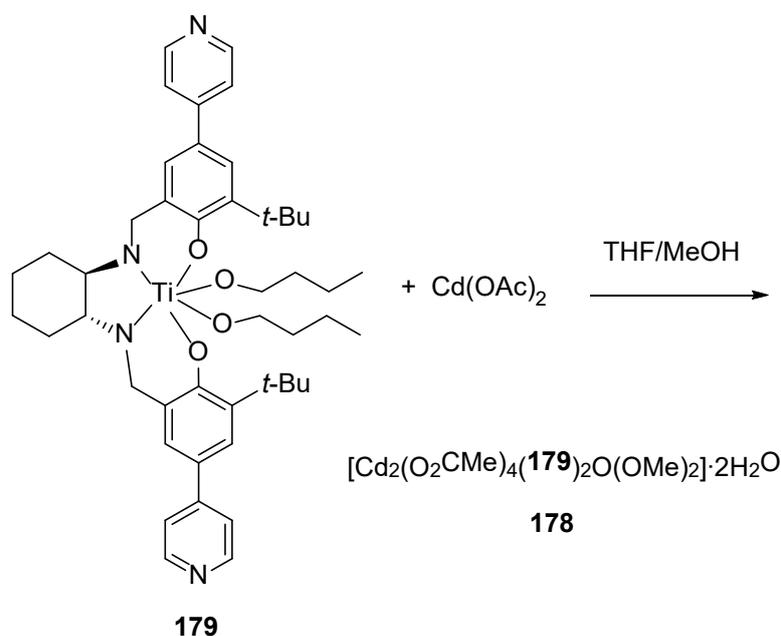
## 9. Miscellaneous enantioselective titanium-catalyzed reactions

A number of asymmetric cyanohydrin formations [135] have been promoted by chiral titanium catalysts [136]. In an example reported in 2015 by Liu and Cui, novel chiral porous

metal-organic frameworks **178** containing  $\mu$ -oxo-bis[Ti(salan)] dimers were employed at 5 mol% of catalyst loading and -10 °C in dibromomethane as the solvent to promote asymmetric cyanation of aldehydes with TMS-CN (Scheme 64) [137]. This catalyst was prepared through solvothermal reaction between Ti(salan)(OBu)<sub>2</sub> **179** and Cd(OAc)<sub>2</sub>. The cyanation of a series of aromatic aldehydes **2** led to the desired chiral cyanohydrin silyl ethers **180** in uniformly high yields (78-89%) and moderate to excellent enantioselectivities (36-90% ee). It must be noted that heterogeneous and recyclable complex **178** represented the first titanium(salan) metal-organic frameworks catalyst displaying efficient asymmetric induction and catalytic activity towards cyanation of aldehydes. Moreover, the enantioselectivities were significantly higher than those obtained by using the corresponding homogeneous catalyst.



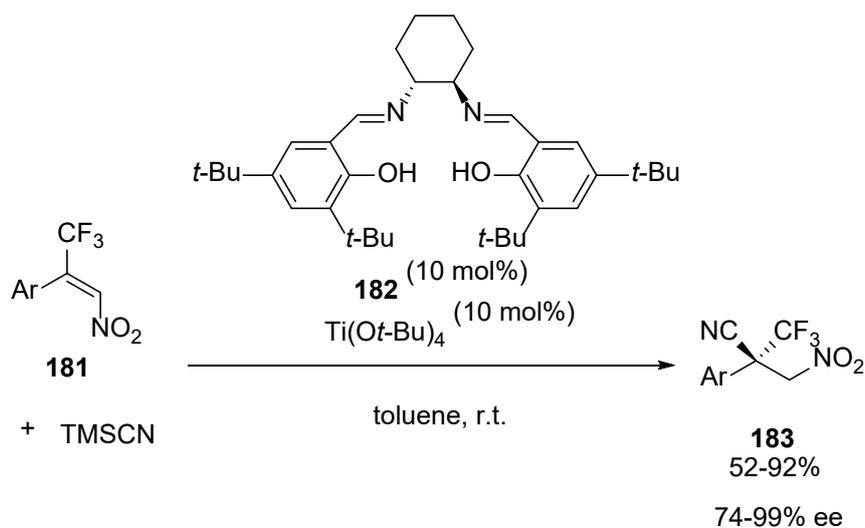
preparation of catalyst:



**Scheme 64.** Cyanation of aromatic aldehydes in the presence of MOFs **178** containing  $\mu$ -oxo-bis[Ti(salan)] dimers [137127].

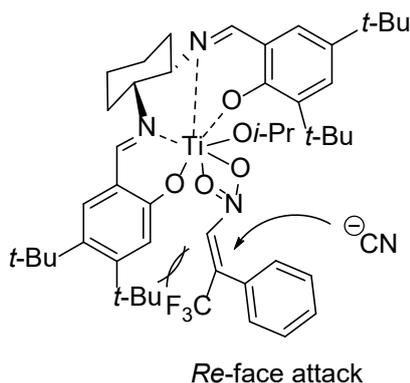
Along with enantioselective catalytic cyanation of carbonyl compounds, the asymmetric catalytic conjugated cyanation of activated olefins has been less developed. In particular, salen ligands have been applied in enantioselective titanium-catalyzed cyanations of nitroolefins [138]. In 2016, the first efficient enantioselective cyanation of  $\beta$ -trifluoromethyl- $\beta$ -disubstituted nitroalkenes using TMSCN was disclosed by Khan et al. [139]. This Michael addition of TMSCN to aromatic trifluoromethylated nitroolefins **181** was catalyzed at room temperature by 10 mol% of Ti(*O*-*t*-Bu)<sub>4</sub> and salen ligand **182** in toluene as solvent. It afforded

a range of chiral  $\beta$ -nitronitriles **183**, containing a carbon quaternary stereocenter exhibiting a trifluoromethyl group, in good to high yields (52-92%) and high enantioselectivities (74-99% ee), as depicted in Scheme 65. Electron-withdrawing and electron-donating could be present at different positions of the phenyl ring of the nitroalkenes, providing comparable results. Some of these products could be easily converted into challenging  $\alpha,\alpha'$ -disubstituted  $\beta$ -amino acids constituting important compounds in pharmaceuticals [140]. A possible transition state is depicted in Scheme 65 in which the nitro group of the alkene coordinates to titanium (IV). Because of the presence of the *t*-butyl groups on the catalyst, the cyanide attacks at the  $\beta$ -position of the nitroalkene through the *Re*-face.



Ar = Ph, *m*-Tol, *p*-Tol, *o*-MeOC<sub>6</sub>H<sub>4</sub>, *p*-MeOC<sub>6</sub>H<sub>4</sub>, *p*-ClC<sub>6</sub>H<sub>4</sub>,  
*p*-FC<sub>6</sub>H<sub>4</sub>, *m*-FC<sub>6</sub>H<sub>4</sub>, *o*-FC<sub>6</sub>H<sub>4</sub>, 3,4-F<sub>2</sub>C<sub>6</sub>H<sub>3</sub>, *m*-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>

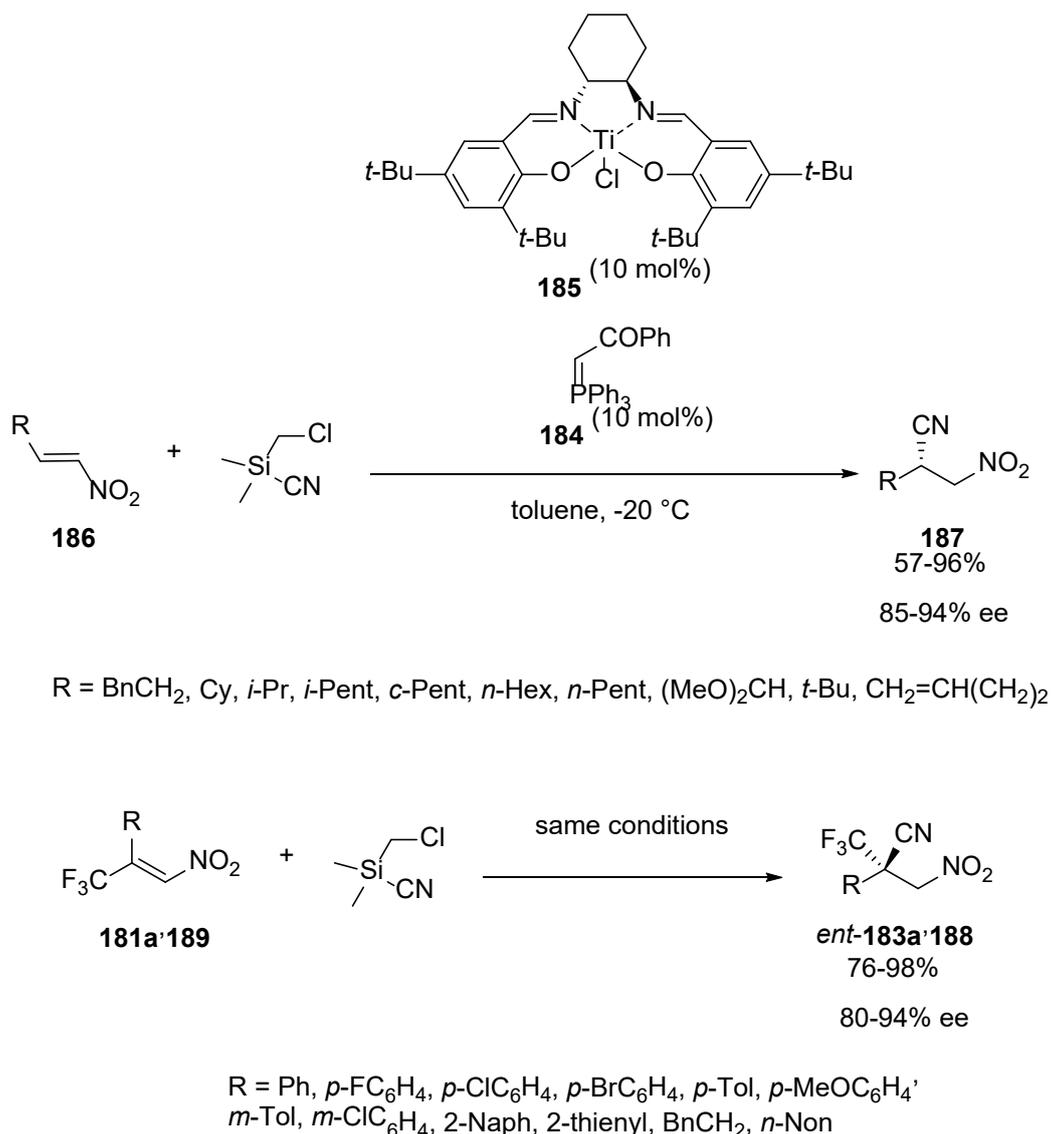
proposed transition state (with Ar = Ph):



**Scheme 65.** Michael addition of  $\text{TMSCN}$  to trifluoromethylated nitroolefins in the presence of salen ligand **182** [139127].

Later in 2020, Zhou et al. demonstrated that phosphorane **184** could efficiently activate (salen)- $\text{TiCl}_2$  complex **185** to achieve excellent enantioselectivities in the cyanation of nitroolefins with  $\text{Me}_2(\text{CH}_2\text{Cl})\text{SiCN}$  as the cyanating reagent (Scheme 66) [141]. The reaction involved at  $-20\text{ }^\circ\text{C}$  10 mol% of precatalyst **185** and the same quantity of phosphorane **184** as an additive in toluene as solvent. The asymmetric cyanation of a range of  $\beta$ -aliphatic nitroolefins **186** led to the corresponding chiral tertiary  $\beta$ -nitronitriles **187** in good to quantitative yields (57-96%) and uniformly high enantioselectivities (85-94% ee). Similarly,

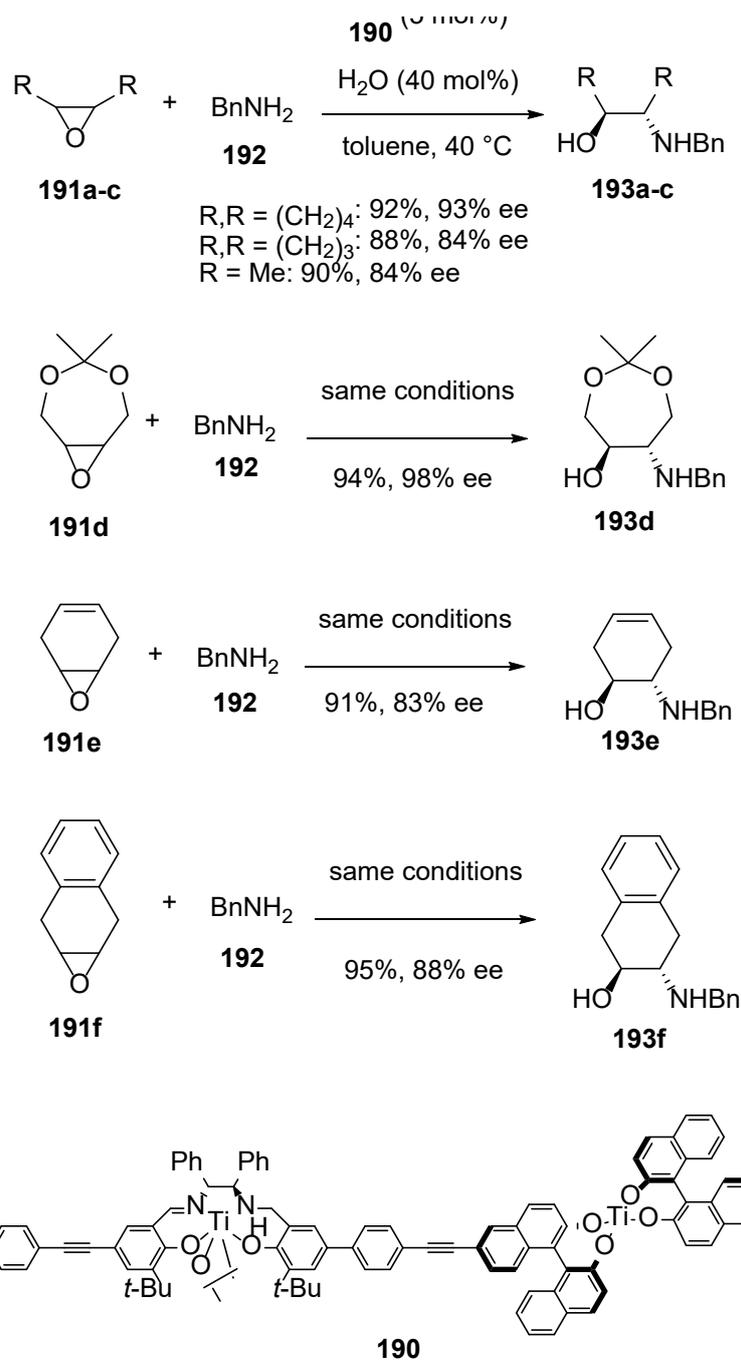
chiral quaternary  $\beta$ -nitronitriles *ent*-**183a,188** were produced with comparable excellent results (76-98% yields, 80-94% ee) from the corresponding  $\beta$ -trifluoromethylated nitroolefins **181a,189** bearing either a  $\beta$ -aryl or  $\beta$ -alkyl substituent. In addition to its wide substrate scope, this novel methodology constituted the first example of activating a (salen) titanium complex by phosphoranes in asymmetric catalysis.



**Scheme 66.** Michael additions of Me<sub>2</sub>(ClCH<sub>2</sub>)SiCN to nitroolefins in the presence of phosphorane-activated salen catalyst **185** [141127].

In another context, the desymmetrization of *meso*-epoxides through asymmetric ring-opening with nucleophiles, such as amines [142], has been catalyzed by various types of

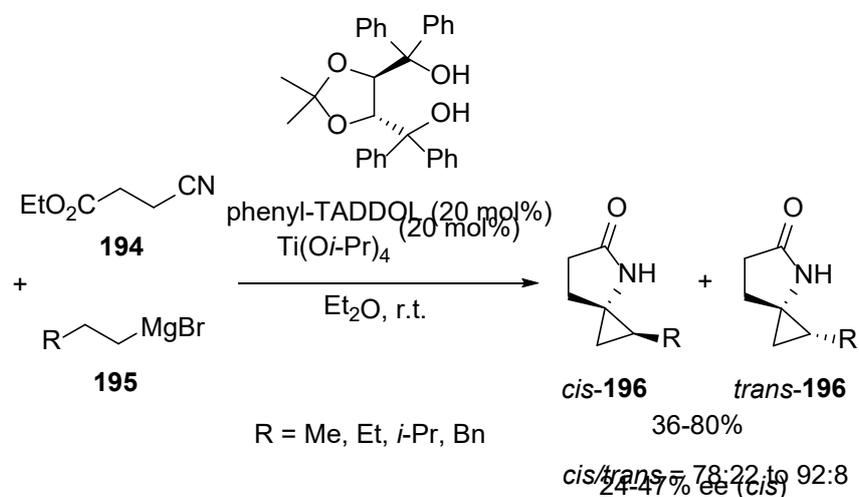
chiral titanium catalysts derived from salen, Schiff bases and BINOL derivatives among other ligands [143]. These methodologies allow important building blocks in synthesis which are chiral  $\beta$ -amino alcohols to be easily synthesized [144]. In 2017, Tu et al. reported the synthesis of a novel type of heterogeneous titanium catalysts, such as robust and self-supported titanium complex **190** [145]. Its synthesis involved linkage between oxygen-bridging BINOLate and salen ligands, providing the corresponding heteroditopic ligand. The latter further reacted with  $\text{Ti}(\text{O}i\text{-Pr})_4$  to lead through coordination polymerization to catalyst **190** including two types of chiral titanium moieties. This novel stable complex was investigated to promote the ring-opening of various *meso*-epoxides **191a-f** with benzylic amine **192** at 5 mol% of catalyst loading in toluene as solvent. Performed at 40 °C in the presence of water as an additive, the reaction afforded chiral  $\beta$ -amino alcohols **193a-f** in both excellent yields (88-95%) and enantioselectivities (83-98% ee), as shown in Scheme 67. It must be noted that the high stable catalyst could be reused up to 20 times without losing catalytic activity and enantioselectivity.



**Scheme 67.** Ring-openings of *meso*-epoxides with benzylic amine in the presence of self-supported catalyst **190** [145127].

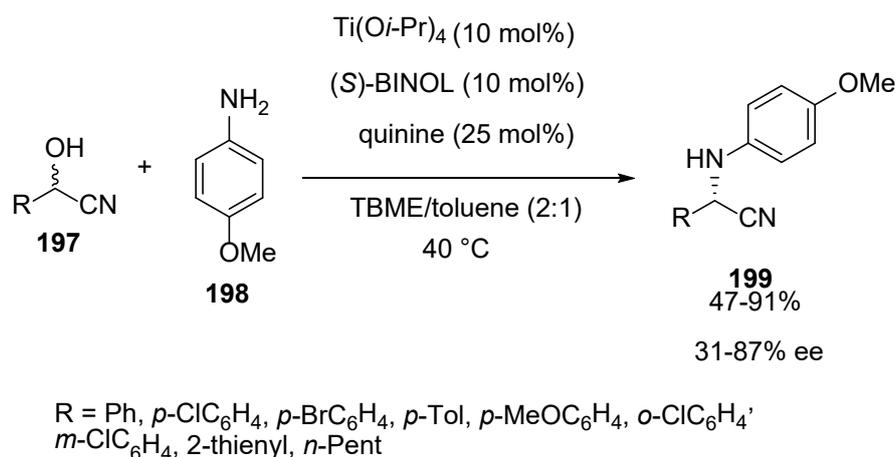
In 2018, Bertus et al. developed the first enantioselective titanium-catalyzed cyclopropanation of cyanoester **194** with Grignard reagents **195** [146]. Among a variety of chiral ligands investigated in combination with 20 mol% of Ti(O*i*-Pr)<sub>4</sub>, phenyl-TADDOL

ligand employed at the same catalyst loading was found optimal. Performed in diethylether as the solvent, the reaction afforded the corresponding enantioenriched spirocyclopropanelactams **196** as mixtures of *cis*- and *trans*-diastereomers with both moderate to high yields (36-80%) and *trans*-diastereoselectivities (56-84% de). As illustrated in Scheme 68, the major *trans*-diastereomers were obtained with low to moderate enantioselectivities (24-47% ee).



**Scheme 68.** Cyclopropanation of a cyanoester with Grignard reagents in the presence of phenyl-TADDOL [146127].

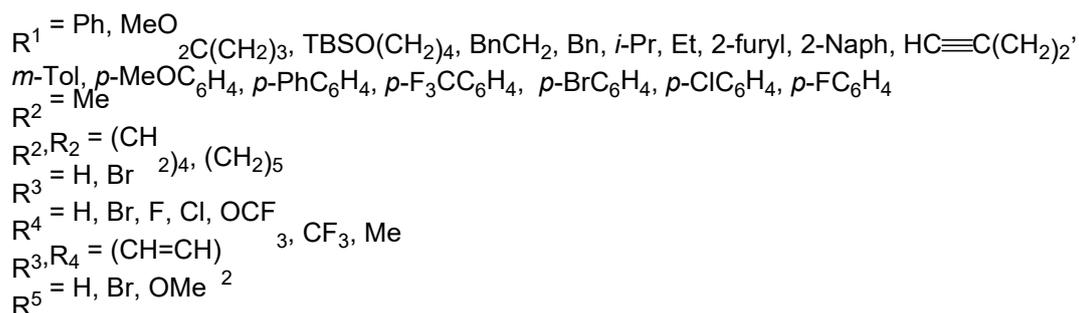
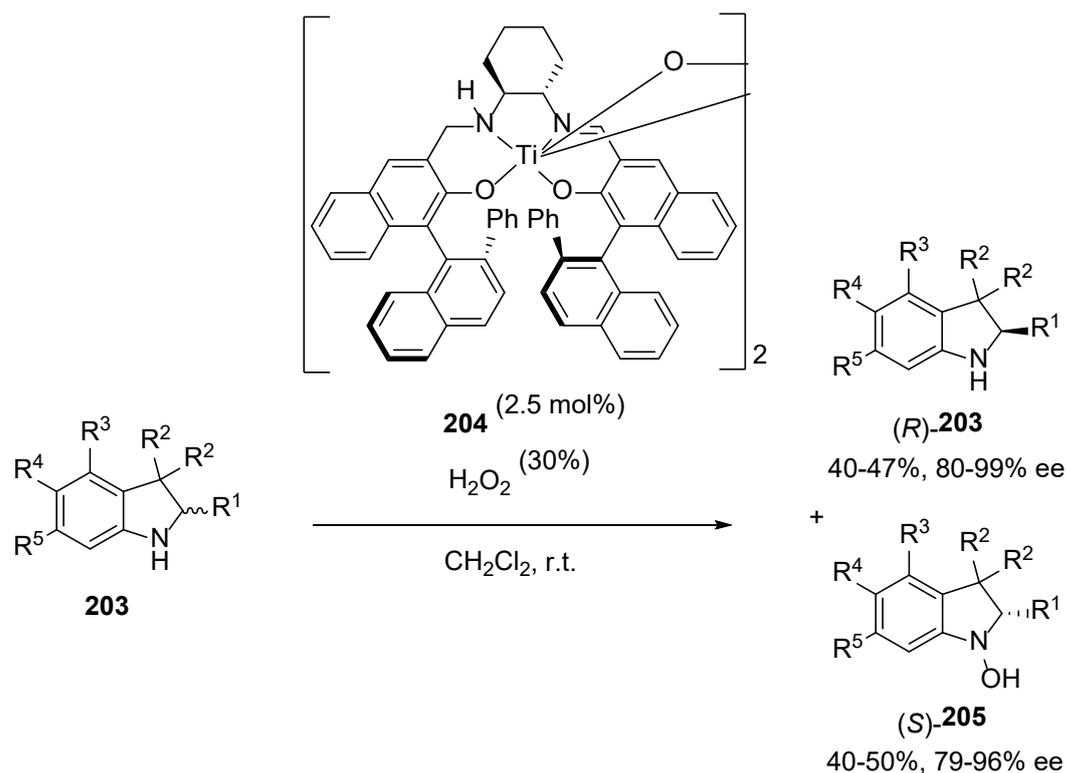
$\alpha$ -Aminonitriles constitute precious precursors of  $\alpha$ -amino acids, peptides and proteins in addition to many drugs [147]. In 2020, Peng and Liu disclosed a novel simple methodology to prepare these products based on a direct asymmetric amination of cyanohydrins [148]. The reaction was catalyzed at 40 °C with a catalyst system composed of 10 mol% of  $\text{Ti}(\text{O}i\text{-Pr})_4$  and (*S*)-BINOL and 25 mol% of quinine. Performed in a 2:1 mixture of MTBE and toluene as solvent, the reaction of aromatic, heteroaromatic and aliphatic cyanohydrins **197** with *p*-methoxybenzyl amine **198** gave rise to chiral  $\alpha$ -aminonitriles **199** in good yields (47-91%) and moderate to high enantioselectivities (31-87% ee), as illustrated in Scheme 69.



**Scheme 69.** Amination of cyanohydrins with *p*-methoxybenzyl amine in the presence of (*S*)-BINOL and quinine [148127].

In 2019, Michaelis et al. described the synthesis of novel chiral phosphoramidate titanium catalyst **200** to be used in asymmetric intramolecular allylic amination of hindered amine **201** into chiral piperidine **202** [149]. Actually, titanium complex **200** (5 mol%) was assembled to [Pd(Methallyl)Cl]<sub>2</sub> (2.5 mol%) to give an in situ generated heterobimetallic Ti/Pd complex which was the real catalyst of the process. In the presence of 5 mol% of AgOTf and TEA, the reaction occurred to provide quantitatively desired chiral piperidine **202** in 36% ee (Scheme 70).

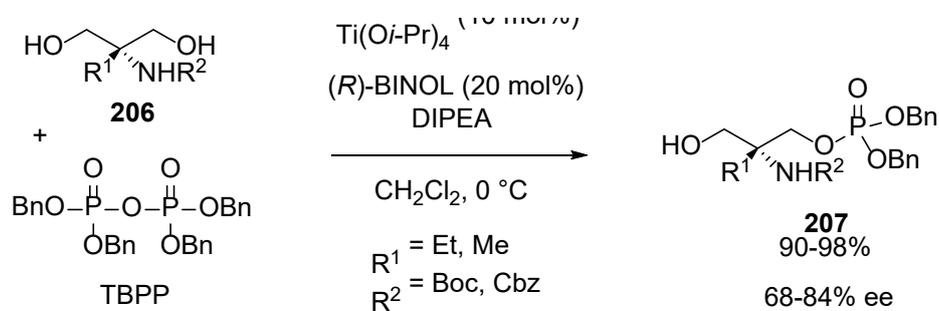




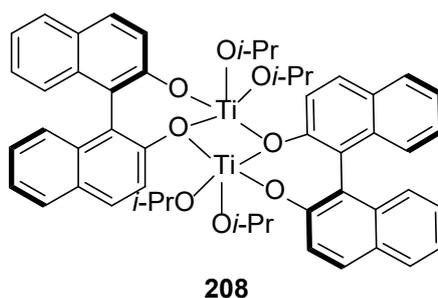
**Scheme 71.** Kinetic resolution of indolines through N–O bond formation in the presence of di- $\mu$ -oxo titanium(salalen) catalyst **204** [151149127].

The same year, Sculimbrene et al. investigated the desymmetrization of 2,2-disubstituted-1,3-diols **206** through phosphorylation in the presence of a titanium catalyst derived from (*R*)-BINOL [152]. As illustrated in Scheme 72, the reaction employed tetrabenzyl pyrophosphate (TBPP) as the phosphorylating agent and was performed at 0 °C in dichloromethane as the solvent. It was catalyzed by a chiral complex in situ generated from 10 mol% of  $\text{Ti}(\text{O}i\text{-Pr})_4$  and 20 mol% of (*R*)-BINOL as ligand in the presence of DIPEA as a base. The

phosphorylation of several 1,3-diols exhibiting a quaternary C2 center including a protected amine led to the corresponding chiral benzyl phosphates **207** with excellent yields (90-98%) and moderate to high enantioselectivities (68-84% ee). According to mechanistic studies, the authors proposed dimeric complex **208** as the active catalyst, which coordinated the diol substrate at both the two hydroxyl groups. The presence of a carbamate carbonyl or nitrogen group on the substrate ( $R^2 = \text{Boc}, \text{Cbz}$ ) and that of an exogenous tertiary amine (DIPEA) in the coordination sphere of the catalyst was found essential for achieving high enantioselectivity.



proposed active catalyst:



**Scheme 72.** Phosphorylation of 2,2-disubstituted-1,3-diols with TBPP in the presence of  $(R)$ -BINOL [152149127].

## 10. Conclusions

This review demonstrates that asymmetric titanium catalysis encounters an amazing development. It updates the field of enantioselective titanium-catalyzed reactions of all types reported since the beginning of 2015, illustrating the power of these green catalysts to provide high stereoselectivity in many types of asymmetric transformations. For example, excellent enantioselectivities (up to >99% ee) have been described in 1,2-nucleophilic alkyl/aryl additions of organozinc, trialkylborane, organolithium, organotitanium, trialkylaluminum, alkylzirconium and Grignard reagents to aldehydes by using in most cases (H<sub>8</sub>)-BIN(M)OL derived ligands including supported ones. Arylations of ketones with organotitanium, trialkylaluminum, organolithium or Grignard reagents performed in the presence of (H<sub>8</sub>)-BINOL-derived ligands but also protected 1,2-aminoalcohol or 1,2-diamine ligands also provided excellent enantioselectivities (up to 98% ee) in these reactions. Furthermore, highly enantioselective additions of organometallic alkynyl derivatives to ketones have allowed the synthesis of chiral propargylic alcohols with up to 96% ee by employing BINOL, quinine or camphor-derived ligands. Allylation and vinylation of aldehydes performed in the presence of (H<sub>8</sub>)-BINOL-derived ligands provided enantioselectivities of up to 90% ee. However, in spite of these excellent results these reactions suffered in most cases from the need of using superstoichiometric amounts of titanium. Along with 1,2-nucleophilic additions to carbonyl compounds, a second class of reactions widely developed in the last few years deals with asymmetric sulfoxidation. Various types of chiral titanium catalysts have been recently employed to promote the enantioselective oxidation of sulfides into chiral sulfoxides using alkyl hydroperoxides as well as hydrogen peroxide as oxidant. Concerning the use of alkyl hydroperoxides, such as cumene or *tert*-butyl hydroperoxide, excellent enantioselectivities of up to >99% ee were recently reported by using tartrate, hydrobenzoin, macrolide and 8-quinolinol-based ligands. The more challenging cheaper and greener oxidant hydrogen peroxide also gave excellent results (up to >99% ee) in asymmetric titanium-catalyzed

sulfoxidations performed in the presence of different types of ligands, such as salens, salans, and salalens including supported ones. This oxidant has also been successfully applied in the last few years in a third class of reactions, that are asymmetric titanium-catalyzed epoxidations of either non-conjugated or conjugated olefins performed with salanen and salan ligands with excellent enantioselectivities (up to >99% ee). Other types of ligands, such as hydroquinine-derived Schiff bases and 8-quinolinol-based ligands, provided comparable enantioselectivities (up to 97% ee) in these reactions using alkyl hydroperoxides as oxidants. The synthesis of important chiral epoxides have also been achieved with high enantioselectivities (99% ee) through asymmetric titanium-catalyzed Darzens reactions of aldehydes/isatins with diazoacetamides by using BINOL or 1,16-dihydroxytetraphenylene ligands. In addition, chiral titanium catalysts derived from  $\beta$ -dihydroxyamide, binaphthyl carboxylic acid and macrocyclic salen ligands were successfully applied to promote a fourth class of reactions which are reductions, including ketone reductions, intramolecular hydroalkoxylations and intramolecular hydrophosphonylations, with up to 98%, 87% and 98% ee, respectively. The economic interest in combining asymmetric titanium catalysis with the concept of modern economic one-pot domino reactions is obvious. Meanwhile, it is only in the last decade that the first examples of enantioselective titanium-catalyzed domino reactions have been disclosed. Recently, different types of these fascinating reactions have been described, such as domino Knoevenagel/hetero-Diels–Alder cycloaddition reactions of cyclic 1,3-dicarbonyl compounds with aldehydes performed with up to 99% ee in the presence of BINOL-derived ligands; domino 1,2-addition/Michael/lactonization reactions of 2-arylvinylcinnamaldehydes with aldehydes with >99% ee by using a chiral N-heterocyclic carbene catalyst; and domino epoxidation/cyclization reactions of  $\beta,\gamma$ -unsaturated carboxylic acids with up to 97% ee in the presence of a BINOL-derived ligand. In another area, several good results were described in a sixth class of reactions that are cycloadditions. Indeed,

hetero-Diels–Alder cycloadditions of aromatic aldehydes with 2,3-dimethylbutadiene performed in the presence of a (*R*)-BINOL-derived titanium catalyst occurred with up to 95% ee while simple Diels–Alder cycloadditions of carboxylic ester dienophiles with 1,3-dienes provided enantioselectivities of up to 89% ee when using a 1,2-diol-derived titanium catalyst. A seventh class of reactions recently developed with success are dihalogenations of alkenes, such as the first bromochlorination of allylic alcohols performed with complete regioselectivity in the presence of a Schiff base ligand with up to 97% ee. Moreover, excellent enantioselectivities were also disclosed in other types of reactions, such as cyanations of aldehydes achieved with 90% ee in the presence of MOFs containing  $\mu$ -oxo-bis[Ti(salan)] dimers; Michael additions of TMSCN to trifluoromethylated nitroolefins providing 99% ee in the presence of a salen ligand; or ring-openings of *meso*-epoxides with amines giving up to 98% ee by using a self-supported titanium catalyst among other transformations. In spite of these impressive advances, many challenges remain, such as better understanding the mechanisms of the reactions, improving the scope of some processes, decreasing the quantity of catalyst loadings, and discerning the role of the aggregation of titanium complexes. With the aim of developing a more environmentally friendly chemistry, chemists will be more and more invited to use catalysts based on more abundant first-row transition metals such as titanium. Consequently, the development of novel chiral titanium catalytic systems to promote all type of asymmetric organic reactions is undeniable in the future as well as their application in the total synthesis of important products.

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