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Recent developments in enantioselective lanthanide-catalyzed transformations

Helene Pellissier

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Recent developments in enantioselective lanthanide-catalyzed transformations

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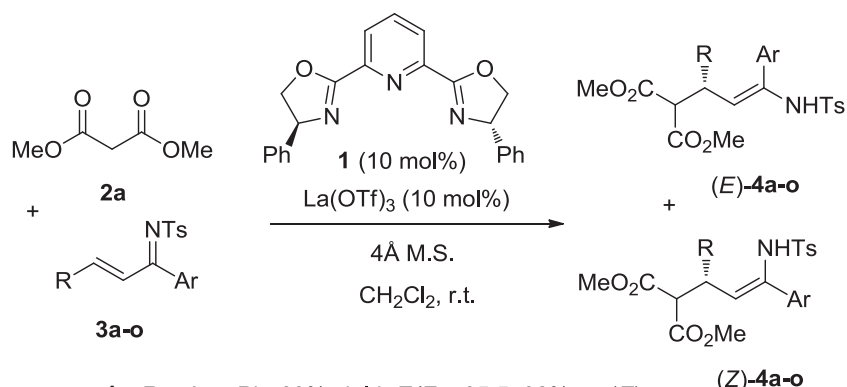
Abbreviations: Ar, aryl; BINOL, 1,1'-bi-2-naphthol; Bpy, 2,2'-bipyridyl; Bn, benzyl; BNP, Binaphthophosphole; Boc, *tert*-butoxycarbonyl; BSA, bis-(trimethylsilyl)acetamide; CB, carbon black; cod, 1,5-cyclooctadiene; Cy, cyclohexyl; DBDMH, 1,3-dibromo-5,5-dimethylhydantoin; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DCE, dichloroethane; de, diastereomeric excess; DMAP, 4-(dimethylamino)pyridine; DMF, *N,N*-dimethylformamide; ee, enantiomeric excess; EPR, electron paramagnetic resonance; EWG, electron-withdrawing group; Hex, hexyl; HFIP, hexafluoroisopropanol; HMDS, hexamethyldisilazide; L, ligand; LUMO, lowest occupied molecular orbital; M, metal; Ms, mesityl(2,4,6-trimethylphenyl); M.S., molecular sieves; MWNT, multiwalled carbon nanotube; Naph, naphthyl; NMR, nuclear magnetic resonance; NOBIN, 2-amino-2-hydroxy-1,1'-binaphthalene; Oct, octyl; Pent, pentyl; PI, polymer-incarcerated; PMB, *p*-methoxybenzoyl; Pybox, 2,6-bis(2-oxazolyl)pyridine; RE, rare earth; r.t., room temperature; salen, 1,2-bis(salicylidenamino)ethane; TBHP, *tert*-butylhydroperoxide; TCE, 1,1,2,2-tetrachloroethane; Tf, trifluoromethanesulfonyl; THF, tetrahydrofuran; TIPS, triisopropylsilyl; TMS, trimethylsilyl; Tol, tolyl; Ts, 4-toluenesulfonyl (tosyl); Val, valine.

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1. Introduction

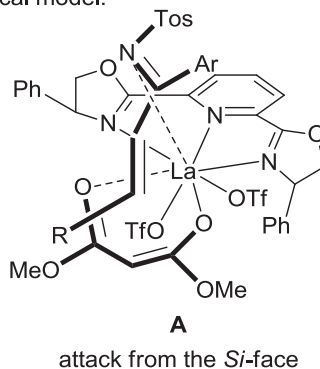
Asymmetric catalysis of organic reactions constitutes an important field in modern science and technology [1]. While asymmetric catalysts containing p-block metal elements or d-block elements have been extensively investigated [1d,e], the use of f-block elements, such as lanthanides, as metal components for asymmetric Lewis acid catalysts has been underestimated for a long time. The use of lanthanides (scandium, yttrium, and lanthanum will be included as lanthanides in this review for brevity) in asymmetric catalysis was first reported by Danishefsky et al. in 1983 who obtained moderate enantioselectivities of up to

58% ee in europium-catalyzed hetero-Diels–Alder reactions [2]. Ever since, the involvement of chiral lanthanide complexes as new catalysts in asymmetric synthesis has become of intense interest related to their unique chemical and physical properties. For example, because of their large ionic radii, lanthanide complexes can exhibit high coordination numbers of six or greater (up to 12) while keeping their Lewis acidity in contrast with conventional Lewis acids that sometimes lose their activities as a result of coordinative saturation. These properties are highly advantageous for assembling various chiral ligands around the metals, allowing the construction of structurally sophisticated complexes to be achieved with an integrated chiral space in which the stereochemistry of the reaction may



- 4a: R = Ar = Ph: 63% yield, *E/Z* = 95:5, 92% ee (*E*)
 4b: R = *p*-FC₆H₄, Ar = Ph: 66% yield, *E/Z* = 97:3, 90% ee (*E*)
 4c: R = *p*-ClC₆H₄, Ar = Ph: 93% yield, *E/Z* = 88:12, 86% ee (*E*)
 4d: R = *p*-BrC₆H₄, Ar = Ph: 99% yield, *E/Z* = 77:23, 85% ee (*E*)
 4e: R = *p*-O₂NC₆H₄, Ar = Ph: 97% yield, *E/Z* = 87:13, 90% ee (*E*)
 4f: R = *p*-MeOC₆H₄, Ar = Ph: 80% yield, *E/Z* = 71:29, 69% ee (*E*)
 4g: R = 2-furanyl, Ar = Ph: 78% yield, *E/Z* = 79:21, 94% ee (*E*)
 4h: R = 3-furanyl, Ar = Ph: 66% yield, *E/Z* = 84:16, 85% ee (*E*)
 4i: R = Me, Ar = Ph: 98% yield, *E/Z* = 88:12, 75% ee (*E*)
 4j: R = Ph, Ar = *p*-FC₆H₄: 67% yield, *E/Z* = 88:12, 86% ee (*E*)
 4k: R = Ph, Ar = *p*-ClC₆H₄: 80% yield, *E/Z* = 84:16, 80% ee (*E*)
 4l: R = Ph, Ar = *p*-O₂NC₆H₄: 84% yield, *E/Z* = 80:20, 82% ee (*E*)
 4m: R = Ph, Ar = *p*-MeOC₆H₄: 86% yield, *E/Z* = 71:29, 80% ee (*E*)
 4n: R = Ph, Ar = *o*-FC₆H₄: 84% yield, *E/Z* = 76:24, 82% ee (*E*)
 4o: R = Ph, Ar = *m*-O₂NC₆H₄: 99% yield, *E/Z* = 82:18, 84% ee (*E*)

proposed stereochemical model:



Scheme 1. Lanthanum-catalyzed Michael addition of dimethyl malonate to α,β -unsaturated *N*-tosyl imines [9].

effectively be controlled. The goal of this review is to collect the major developments in all types of enantioselective lanthanide-catalyzed transformations published since the beginning of 2012, since this field was most recently reviewed by Mori and Kobayashi in a book chapter published in 2012, covering the literature up to 2011 [3]. It must be noted that the special coverage of enantioselective scandium- and yttrium-catalyzed asymmetric reactions is limited to the year 2016 since two recent reviews published in 2016 included literature up to 2015 [4]. Previous to 2012, and more generally, the field of (racemic) rare earth metal catalysis has been reviewed by various authors [5]. Moreover, several accounts were reported by Shibasaki et al. [6]. The review is divided into eleven parts, dealing successively with enantioselective lanthanide-catalyzed Michael reactions, enantioselective lanthanide-catalyzed cycloaddition reactions, enantioselective lanthanide-catalyzed aldol-type reactions, enantioselective lanthanide-catalyzed epoxidation reactions of alkenes, enantioselective lanthanide-catalyzed Mannich-type reactions, enantioselective lanthanide-catalyzed 1,2-nucleophilic additions to carbonyl compounds and imines, enantioselective lanthanide-catalyzed Friedel–Crafts reactions, enantioselective lanthanide-catalyzed hydroamination reactions, enantioselective lanthanide-catalyzed ring-opening reactions, enantioselective lanthanide-catalyzed domino and tandem reactions, and miscellaneous enantioselective lanthanide-catalyzed reactions.

2. Enantioselective lanthanide-catalyzed Michael reactions

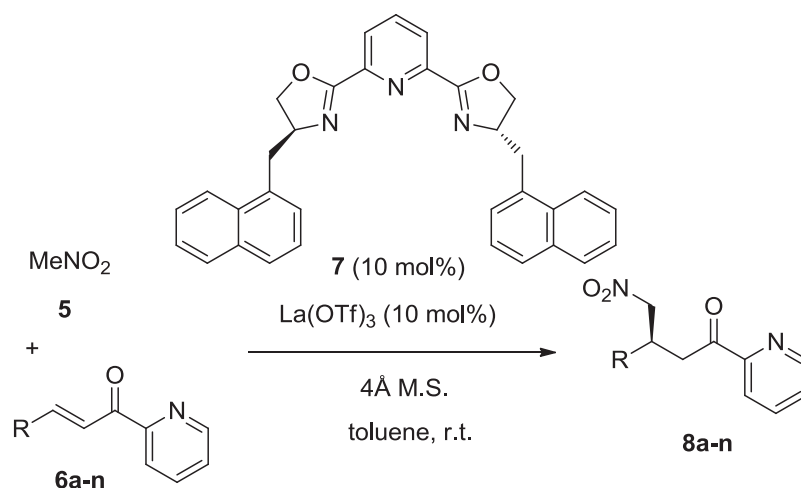
The conjugate addition of nucleophiles to electron-poor alkenes plays an important role in organic synthesis by allowing carbon-carbon and carbon-heteroatom bond-forming reactions to be easily achieved [7]. Consequently, many different versions of this transformation including asymmetric ones have been reported, using a wide variety of nucleophiles, conjugate acceptors as well as catalysts. Besides the growing success of organocatalysts to promote these reactions [8], rare earth metal chiral catalysts have also been successfully employed in the last two decades. In particular, many remarkable results have been described by using chiral scandium and yttrium catalysts [4]. Among other chiral lanthanide complexes recently applied to these reactions, a Pybox chiral lanthanum complex, in situ generated from La(OTf)₃ and chiral Pybox ligand **1**, was employed by Blay and Pedro to catalyze the first asymmetric Michael addition of dimethyl malonate **2a** to α,β -unsaturated *N*-tosyl imines **3a–o** [9]. As shown in Scheme 1, the reaction performed at room temperature in dichloromethane as solvent led to the corresponding chiral γ -dehydro- δ -amino diesters **4a–o** bearing a stereogenic center at the allylic position as mixtures of *E*- and *Z*-diastereomers. The *E*-diastereomers were obtained in good to quantitative yields (63–99%) as major ones with diastereoselectivities ranging from 42 to 94% de combined with enantioselectivities of 69 to 92% ee. Notably, no cyclization to the corresponding lactams was observed under the reaction conditions. A range of imines **3a–f** bearing an aromatic ring attached to the β -carbon atom substituted with either electron-donating or electron-withdrawing substituents were compatible to the process, leading to the expected products **4a–f** with good to high diastereo- and enantioselectivities of up to 94% de and 92% ee, respectively. Moreover, heteroaromatic imines **3g–h** provided the corresponding products **4g–h** in 66–78% yields, moderate diastereoselectivities of 58–68% de along with high enantioselectivities of 85–94% ee. The scope of the process was also extended to alkyl imine **3i** (R = Me) that gave product **4i** in quantitative yield, 76% de, and 75% ee. The aryl group attached to the imine (Ar) was also amenable to variation. Aromatic rings bearing either electron-donating or electron-withdrawing groups were permitted without

much influence on the enantioselectivity of the reaction (80–86% ee for products **4j–o**). The results indicated the preference of dimethyl malonate **2a** to attack from the *Si* face of the double bond of the unsaturated imine **3**. Consequently, the mechanism involved an octa-coordinated La(III) species **A** with both the 1,3-dicarbonyl compound and the imine coordinated to the metal center (Scheme 1). In this complex, the imine in its *s-trans* conformation was oriented to avoid the steric interaction of the aryl (Ar) and tosyl groups with the phenyl group of the ligand, thus leading to the Michael product **4** exhibiting the *R* configuration at the stereogenic center and the *E* geometry at the double bond. The synthetic utility of this novel methodology was demonstrated in the preparation of optically active δ -aminoesters and lactams.

On the other hand, the conjugate addition of nucleophiles to α,β -unsaturated ketones has attracted more attention than that to α,β -unsaturated imines because of the higher electrophilicity of the ketone substrates, and the fact that the latter substrates allow a better control of the regioselectivity in the addition reaction. Indeed, α,β -unsaturated imines are ambident electrophiles that can either undergo 1,2- or 1,4-nucleophilic addition processes. In this context, the same group developed enantioselective lanthanum-catalyzed Michael additions of nitromethane **5** to a range of (*E*)-2-azachalcones **6a–l** [10]. When performed in toluene at room temperature and catalyzed by another chiral Pybox lanthanum catalyst, in situ generated from La(OTf)₃ and ligand **7**, the process led to the corresponding chiral nitro-Michael products **8a–n** in good yields (58–74%) and enantioselectivities of up to 82% ee (Scheme 2). This work constituted the first catalytic enantioselective nitro-Michael reaction with (*E*)-2-azachalcones using lanthanum(III)/Pybox complexes as catalysts. The substituent on the β -carbon of the double bond was amenable to variation. Indeed, azachalcones bearing aromatic rings substituted in different positions with either electron-withdrawing or electron-donating groups could be used as substrates in the process, providing the corresponding products **8a–h** with comparable good enantioselectivities (73–82% ee) regardless of the electronic features or position of the substituent. A bulky 1-naphthyl group as well as electron-rich heterocyclic groups was also tolerated, giving the expected products **8i–l** with enantioselectivities of 77–81% ee. Moreover, substrates **6m–n** bearing an aliphatic group, such as methyl or bulky *t*-butyl groups, both provided even higher enantioselectivities of 81–87% ee. X-ray crystallographic analysis of product **8f** allowed the absolute stereochemistry of the stereogenic center to be determined as *S* configuration. The stereochemical model depicted in Scheme 2 explains the results in which the nitronate attacks from the *Si* face of the double bond of the azachalcone. In this model, La(III) coordinates three nitrogen atoms from the Pybox ligand, one oxygen and one nitrogen atom from azachalcone **6**, and two triflate ions in apical positions of the cation coordination sphere. The shielding effect exerted by the bulky 1-naphthylmethyl substituent at the 4'-position of the ligand determined the preferential attack from the *Si*-face of the double bond β -carbon.

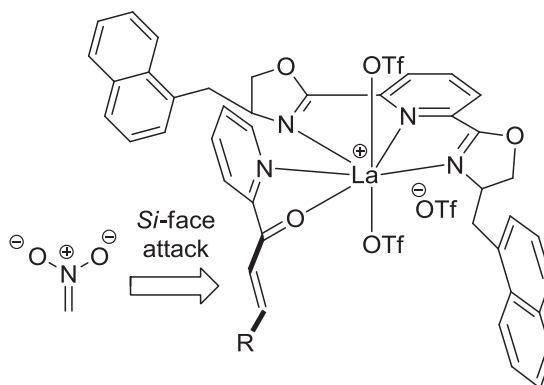
With the aim of extending the scope of the precedent methodology, the use of larger nitroalkanes, such as nitroethane **9a** and nitropropane **9b**, was investigated, albeit it led to the formation of mixtures of *anti*- and *syn*-diastereomers **10a–j** with moderate diastereoselectivities of 12–46% de, favoring the *anti*-diastereomers that were obtained in good enantioselectivities of 51–83% ee (Scheme 3) [10].

In 2014, Xu et al. reported a rare example of asymmetric phospho-Michael addition of diethyl phosphite **11** to chalcones **12a–q** performed in toluene at 0 °C [11]. This process was promoted by a chiral yttrium silylamide catalyst, in situ generated from [(TMS)₂N]₃Yb(μ -Cl)Li(THF)₃ and chiral salen ligand **13**. As shown in Scheme 4, it provided a series of chiral



- 8a:** R = Ph: 74% yield, 79% ee
8b: R = *o*-ClC₆H₄: 69% yield, 73% ee
8c: R = *m*-ClC₆H₄: 58% yield, 82% ee
8d: R = *m*-BrC₆H₄: 68% yield, 78% ee
8e: R = *p*-ClC₆H₄: 73% yield, 77% ee
8f: R = *p*-BrC₆H₄: 74% yield, 79% ee
8g: R = *p*-MeOC₆H₄: 65% yield, 78% ee
8h: R = *p*-O₂NC₆H₄: 70% yield, 74% ee
8i: R = 1-Naph: 68% yield, 77% ee
8j: R = 2-thienyl: 72% yield, 81% ee
8k: R = 3-thienyl: 69% yield, 81% ee
8l: R = 2-furanyl: 68% yield, 79% ee
8m: R = Me: 65% yield, 87% ee
8n: R = *t*-Bu: 72% yield, 81% ee

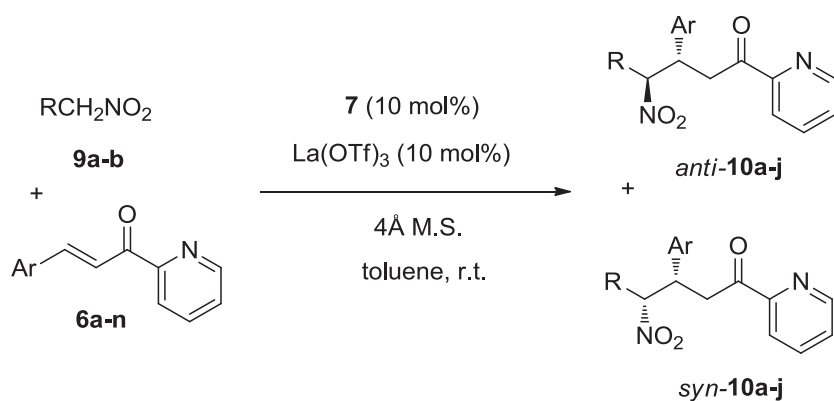
proposed stereochemical model:



Scheme 2. Lanthanum-catalyzed Michael addition of nitromethane to azachalcones and other α,β -unsaturated ketones [10].

γ -oxophosphonates **14a–q** in high yields of 80–94% and enantioselectivities of 82–94% ee. To study the influence of the central metal, a series of lanthanide silylamide complexes derived from ligand **13** were investigated in the reaction, showing that ytterbium catalyst provided higher enantioselectivities than the corresponding lanthanum, neodymium, samarium, and yttrium complexes (51% ee vs 5–36% ee). As shown in [Scheme 4](#), the results were homogeneous for a series of substituted chalcones. Indeed, the electronic properties of the aryl substituents of the chalcones had no obvious effect on the enantioselectivities of the reactions, while the steric

hindrance was important with regard to the enantioselectivity. Therefore, chalcones **12h** and **12k–q** having an *ortho*-substituted phenyl group at the 3-position afforded the corresponding products **14h** and **14k–q** with relatively higher enantioselectivities (91–94% ee). Moreover, 3-naphthyl-substituted and 3-heteroaromatic chalcones **12i–j** reacted smoothly with diethyl phosphite **11** to afford products **14i–j** with enantioselectivities higher than 90% ee. To explain these results, a mechanism is depicted in [Scheme 4](#) in which the initial step of the process involved an in situ protonolytic generation of salen-Yb-N(TMS)₂



- 10a:** Ar = Ph, R = Me: 68% yield, *anti/syn* = 73:27, 81% ee (*anti*), 71% ee (*syn*)
10b: Ar = Ph, R = Et: 50% yield, *anti/syn* = 64:36, 80% ee (*anti*), 72% ee (*syn*)
10c: Ar = *p*-BrC₆H₄, R = Me: 67% yield, *anti/syn* = 76:24, 57% ee (*anti*), 55% ee (*syn*)
10d: Ar = *p*-BrC₆H₄, R = Et: 53% yield, *anti/syn* = 65:35, 51% ee (*anti*), 54% ee (*syn*)
10e: Ar = *p*-MeOC₆H₄, R = Me: 60% yield, *anti/syn* = 69:31, 77% ee (*anti*), 71% ee (*syn*)
10f: Ar = *p*-MeOC₆H₄, R = Et: 50% yield, *anti/syn* = 56:44, 64% ee (*anti*), 61% ee (*syn*)
10g: Ar = *p*-O₂NC₆H₄, R = Me: 66% yield, *anti/syn* = 72:28, 81% ee (*anti*), 79% ee (*syn*)
10h: Ar = *p*-O₂NC₆H₄, R = Et: 54% yield, *anti/syn* = 65:35, 83% ee (*anti*), 57% ee (*syn*)
10i: Ar = 3-thienyl, R = Me: 66% yield, *anti/syn* = 62:38, 81% ee (*anti*), 70% ee (*syn*)
10j: Ar = 3-thienyl, R = Et: 51% yield, *anti/syn* = 73:27, 75% ee (*anti*), 71% ee (*syn*)

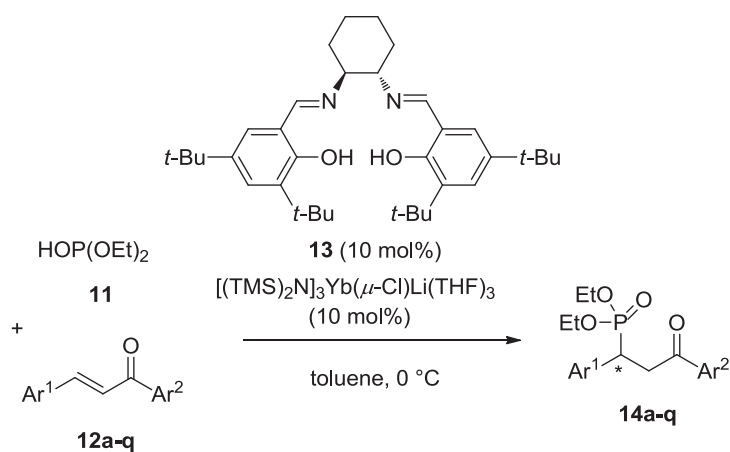
Scheme 3. Lanthanum-catalyzed Michael addition of nitroalkanes to azachalcones [10].

complex **B**. The latter reacted with diethyl phosphite **11** to release HN(TMS)₂ and formed intermediate **C**. As a highly oxophilic Lewis acid, the central ytterbium atom of intermediate **C** coordinated the carbonyl group of the chalcone. Such coordination could both activate the chalcone, and bring closer the enone and the P-nucleophile. This led to a face selective reaction in a chiral environment. The final product **14** was then released through proton exchange between intermediate **D** and another phosphite, while catalyst **B** was regenerated.

In 2015, another ytterbium catalyst, in situ generated from chiral *N,N*-dioxide ligand **15** and Yb(OTf)₃, was developed by Feng et al. [12]. It was further applied to promote the asymmetric vinylogous Michael addition of 3-alkylidene oxindoles **16a–d** to chalcones **12a–s**, delivering the corresponding chiral γ -substituted alkylideneoxindoles **17a–v** in good to excellent yields (66–96%), moderate to good *Z/E* diastereoselectivities (78:22 to 91:9), and high enantioselectivities (84–98% ee). As shown in Scheme 5, electron-withdrawing as well as electron-donating substituents on the aromatic rings Ar¹ and Ar² of chalcones **12** were well tolerated since products **17a–p** were obtained in enantioselectivities $\geq 90\%$ ee. Furthermore, heteroaromatic-substituted product **17r** and fused-ring product **17s** were formed in high yields (77–88%) and enantioselectivities (91–92% ee). The substitution of the benzene ring of the oxindole substrate had also no obvious influence on the enantioselectivity, *Z/E* diastereoselectivity, and yield since products **17t–u** were obtained in 94–98% ee, 85:15 to 89:11 *Z/E* ratio, and 84–88% yield. A benzylidene oxindole (R = Ph) was also successfully employed in the reaction, providing the corresponding product **17v** in 84% yield, 94% ee, and 85:15 *Z/E* ratio.

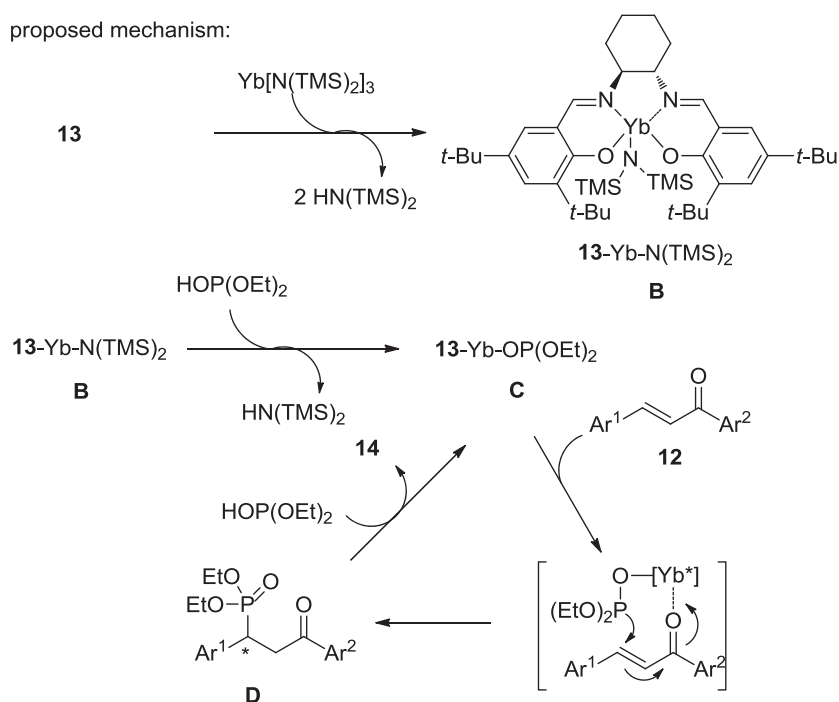
Scandium, which falls in the category of rare earth elements, has chemical properties similar to those of lanthanides, and sometimes exhibit higher catalytic efficiency owing to its higher Lewis acidity arising from a smaller ionic radii. In 1997, Katsuki and Kitajima reported the first asymmetric Michael addition catalyzed by a

chiral scandium complex, dealing with the addition of 2-(trimethylsilyloxy)furans to give chiral butenolides achieved by using Sc(OTf)₃ and 3,3'-bis(diethylaminomethyl)-1,1'-bi-2-naphthol as catalyst system [13]. Ever since, various other ligands have been investigated in scandium-catalyzed Michael additions of β -ketoesters, malonates, hydroxylamines, or thiols to α,β -unsaturated carbonyl compounds, among which *N,N*-dioxides [14], pybox derivatives [15], and BNP ligands [16]. As a recent example, Liu and Feng developed asymmetric scandium-catalyzed Michael additions of malonates **2a–d** to enynes **18a–s** to give the corresponding chiral functionalized trisubstituted allenes **19a–v**, as shown in Scheme 6 [17]. The reaction was performed in the presence of a combination of Sc(OTf)₃ and chiral *N,N*-dioxide **20** that allowed products **19a–v** to be formed in impressive enantioselectivities of 97–99% ee along with good to almost quantitative yields of 61–98% and moderate to high diastereoselectivities of 56–90% de. Notably, enynes tethering aryl as well as alkyl substituents (R¹) on the carbonyl group were suitable substrates, providing comparable good results. Regardless of the electron-withdrawing or electron-donating groups on the 4-position of aromatic rings on the double bond (Ar), there was little influence on the reaction. Indeed, the corresponding products **19f–i** were obtained in high yields (88–94%), excellent diastereoselectivities (84–90% de), and enantioselectivity (99% ee). Various substituents (R³) on the triple bond were also investigated, showing that aryl groups bearing an electron-donating substituent furnished higher diastereoselectivities than electron-withdrawing groups (products **19j–n**). In addition, an enyne containing a 3-thienyl group and another one bearing an *n*-butyl substituent led to the corresponding products **19r** and **19s**, respectively, in 73–90% yields, 97–99% ee, and 78–88% de. A transition state model depicted in Scheme 6 explained the stereoselectivity of the reaction, in which the *Re* face of the enyne was strongly shielded by the nearby benzyl ring. Therefore, the incoming enolate preferred

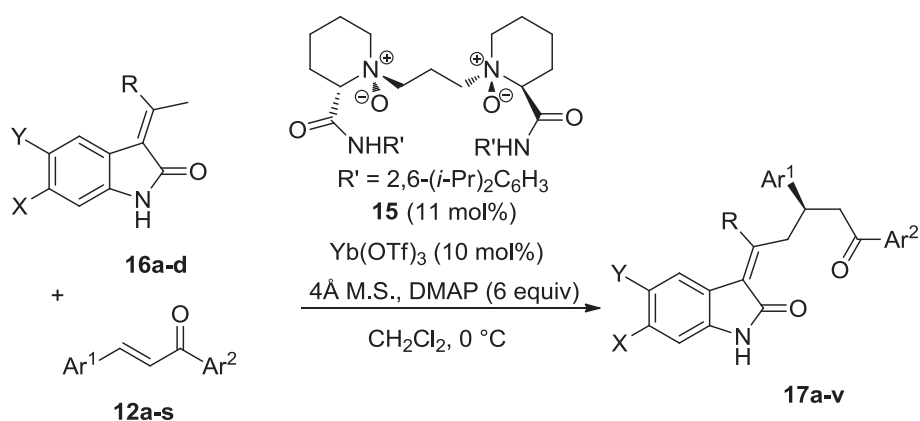


- 14a:** Ar¹ = Ar² = Ph: 94% yield, 89% ee
14b: Ar¹ = Ph, Ar² = *p*-ClC₆H₄: 87% yield, 88% ee
14c: Ar¹ = Ph, Ar² = *p*-MeOC₆H₄: 91% yield, 82% ee (S)
14d: Ar¹ = *o*-MeOC₆H₄, Ar² = Ph: 80% yield, 82% ee
14e: Ar¹ = *p*-ClC₆H₄, Ar² = Ph: 82% yield, 91% ee
14f: Ar¹ = *p*-BrC₆H₄, Ar² = Ph: 82% yield, 90% ee
14g: Ar¹ = *p*-Tol, Ar² = Ph: 88% yield, 86% ee
14h: Ar¹ = *o*-Tol, Ar² = Ph: 84% yield, 94% ee
14i: Ar¹ = 1-Naph, Ar² = Ph: 87% yield, 93% ee
14j: Ar¹ = 2-thienyl, Ar² = Ph: 88% yield, 90% ee
14k: Ar¹ = *o*-Tol, Ar² = *p*-ClC₆H₄: 89% yield, 93% ee
14l: Ar¹ = *o*-Tol, Ar² = *p*-MeOC₆H₄: 86% yield, 91% ee
14m: Ar¹ = 2,6-(Me)₂C₆H₃, Ar² = *p*-Tol: 93% yield, 94% ee
14n: Ar¹ = 2,6-(Me)₂C₆H₃, Ar² = *p*-FC₆H₄: 89% yield, 91% ee
14o: Ar¹ = 2,6-(Me)₂C₆H₃, Ar² = *p*-ClC₆H₄: 87% yield, 94% ee
14p: Ar¹ = 2,6-(Me)₂C₆H₃, Ar² = *p*-BrC₆H₄: 89% yield, 92% ee
14q: Ar¹ = 2,6-(Me)₂C₆H₃, Ar² = *p*-MeOC₆H₄: 91% yield, 92% ee

proposed mechanism:



Scheme 4. Ytterbium-catalyzed phospho-Michael addition of diethyl phosphite to chalcones [11].



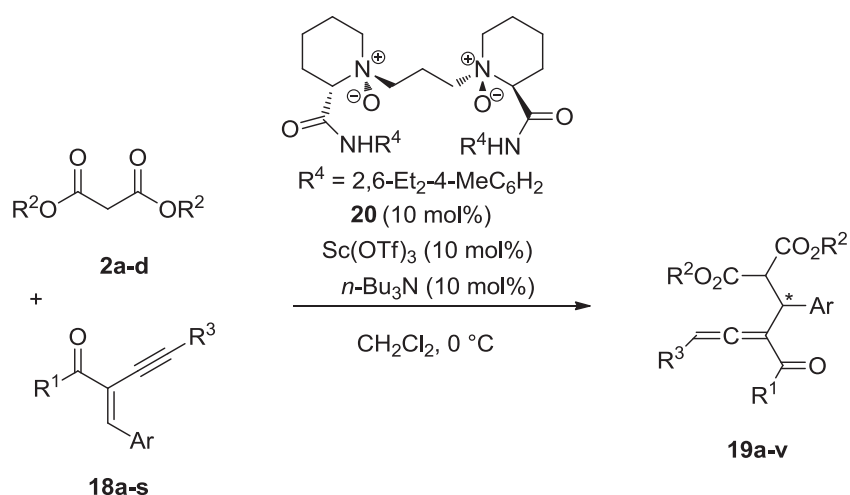
- 17a:** Ar¹ = Ar² = Ph, R = Me, X = Y = H: 88% yield, Z/E = 83:17, 96% ee (Z)
17b: Ar¹ = *p*-FC₆H₄, Ar² = Ph, R = Me, X = Y = H: 83% yield, Z/E = 85:15, 96% ee (Z)
17c: Ar¹ = *p*-ClC₆H₄, Ar² = Ph, R = Me, X = Y = H: 81% yield, Z/E = 90:10, 94% ee (Z)
17d: Ar¹ = *p*-BrC₆H₄, Ar² = Ph, R = Me, X = Y = H: 82% yield, Z/E = 91:9, 90% ee (Z)
17e: Ar¹ = *p*-F₃CC₆H₄, Ar² = Ph, R = Me, X = Y = H: 88% yield, Z/E = 85:15, 90% ee (Z)
17f: Ar¹ = *p*-Tol, Ar² = Ph, R = Me, X = Y = H: 86% yield, Z/E = 83:17, 95% ee (Z)
17g: Ar¹ = *p*-MeOC₆H₄, Ar² = Ph, R = Me, X = Y = H: 86% yield, Z/E = 83:17, 95% ee (Z)
17h: Ar¹ = *m*-ClC₆H₄, Ar² = Ph, R = Me, X = Y = H: 96% yield, Z/E = 87:13, 95% ee (Z)
17i: Ar¹ = *m*-O₂NC₆H₄, Ar² = Ph, R = Me, X = Y = H: 81% yield, Z/E = 82:18, 92% ee (Z)
17j: Ar¹ = *m*-Tol, Ar² = Ph, R = Me, X = Y = H: 88% yield, Z/E = 80:20, 97% ee (Z)
17k: Ar¹ = *m*-PhOC₆H₄, Ar² = Ph, R = Me, X = Y = H: 88% yield, Z/E = 80:20, 97% ee (Z)
17l: Ar¹ = Ph, Ar² = *p*-FC₆H₄, R = Me, X = Y = H: 96% yield, Z/E = 82:18, 96% ee (Z)
17m: Ar¹ = Ph, Ar² = *p*-ClC₆H₄, R = Me, X = Y = H: 83% yield, Z/E = 82:18, 93% ee (Z)
17n: Ar¹ = Ph, Ar² = *p*-BrC₆H₄, R = Me, X = Y = H: 73% yield, Z/E = 78:22, 93% ee (Z)
17o: Ar¹ = Ph, Ar² = *p*-Tol, R = Me, X = Y = H: 67% yield, Z/E = 82:18, 97% ee (Z)
17p: Ar¹ = Ph, Ar² = *p*-MeOC₆H₄, R = Me, X = Y = H: 66% yield, Z/E = 81:19, 96% ee (Z)
17q: Ar¹ = 3,4-Cl₂C₆H₃, Ar² = Ph, R = Me, X = Y = H: 81% yield, Z/E = 84:16, 84% ee (Z)
17r: Ar¹ = 3-thienyl, Ar² = Ph, R = Me, X = Y = H: 77% yield, Z/E = 85:15, 92% ee (Z)
17s: Ar¹ = 3-Naph, Ar² = Ph, R = Me, X = Y = H: 88% yield, Z/E = 86:14, 91% ee (Z)
17t: Ar¹ = Ar² = Ph, R = Me, X = Cl, Y = H: 88% yield, Z/E = 85:15, 98% ee (Z)
17u: Ar¹ = Ar² = Ph, R = Me, X = H, Y = F: 84% yield, Z/E = 89:11, 95% ee (Z)
17v: Ar¹ = Ar² = R = Ph, X = Y = H: 84% yield, Z/E = 85:15, 94% ee (Z)

Scheme 5. Ytterbium-catalyzed Michael addition of 3-alkylidene oxindoles to chalcones [12].

to attack the enyne from the *Si* face. As synthetic applications, some products were easily transformed into furan, and 5-hydroxypyrazoline derivatives, which are important skeletons in many biologically active compounds.

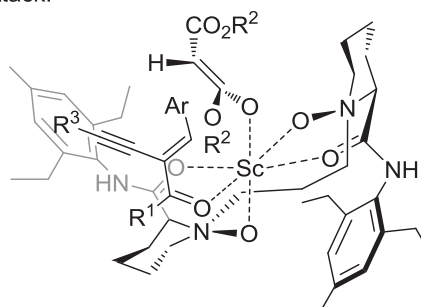
In 2016, Yao et al. reported the synthesis of novel chiral rare earth metal complexes stabilized by chiral phenoxy functionalized prolinolate ligands [18]. Among them, chiral scandium catalyst **21**, preformed by treatment of Sc[N(TMS)₂]₃ with two equivalents of the corresponding ligand in THF at room temperature, was found optimal when applied to promote the asymmetric Michael addition of malonates **2a–d** to chalcones **12a–n**, leading to the corresponding Michael products **22a–q** in high to quantitative yields (80–99%) and moderate to high enantioselectivities (64–90% ee), as shown in Scheme 7. The substrate scope of the reaction included chalcones bearing electron-rich heteroaromatic rings which provided the corresponding products **22p–q** in excellent yields (95–97%) and high enantioselectivities (82–89% ee). The best results were obtained by using diisopropyl malonate as nucleophile in comparison with dimethyl, diethyl, and di(*t*-butyl) malonates (90% ee vs 70–83% ee).

The use of multiple-catalyst systems and multifunctional chiral catalysts has allowed improvements in reactivity and selectivity over traditional catalysts to be achieved, due to cooperative activation of reaction partners [6a,19]. In particular, in lanthanide-catalyzed asymmetric reactions, (hetero)bimetallic systems have been studied extensively [5q,6a–c,19b]. In such systems, one lanthanide metal is used as a Lewis acid to activate an electrophile, and the other metal is used as a nucleophile generator. When dual generation of an activated electrophile and an activated nucleophile takes place at positions defined by the chiral catalyst, the direction of the new bond formation will be controlled with good face- and position-selectivity. Shibasaki's heterobimetallic complexes [M₃(THF)_n][(BINOLate)₃RE] called REMB complexes, containing a rare earth metal (RE), three alkali metals (M), and three BINOLs (RE = Sc, Y, La-Lu; M = Li, Na, K; B = 1,1'-bi-2-naphtholate; RE/M/B = 1/3/3) are the most successful heterobimetallic catalysts, where simple modulation of RE, M, and BINOLate substitution patterns produces a diverse library of powerful catalysts. These privileged frameworks have been applied to catalyze the formation of carbon–carbon and



- 19a:** $R^1 = R^3 = \text{Ar} = \text{Ph}$, $R^2 = \text{Et}$: 85% yield, 84% de, 99% ee
19b: $R^1 = m\text{-Tol}$, $R^2 = \text{Et}$, $R^3 = \text{Ar} = \text{Ph}$: 84% yield, 82% de, 99% ee
19c: $R^1 = m\text{-ClC}_6\text{H}_4$, $R^2 = \text{Et}$, $R^3 = \text{Ar} = \text{Ph}$: 98% yield, 82% de, 99% ee
19d: $R^1 = \text{Me}$, $R^2 = \text{Et}$, $R^3 = \text{Ar} = \text{Ph}$: 92% yield, 78% de, 98% ee
19e: $R^1 = R^3 = \text{Ph}$, $\text{Ar} = o\text{-ClC}_6\text{H}_4$, $R^2 = \text{Et}$: 77% yield, 56% de, 97% ee
19f: $R^1 = R^3 = \text{Ph}$, $\text{Ar} = p\text{-ClC}_6\text{H}_4$, $R^2 = \text{Et}$: 90% yield, 84% de, 99% ee
19g: $R^1 = R^3 = \text{Ph}$, $\text{Ar} = p\text{-BrC}_6\text{H}_4$, $R^2 = \text{Et}$: 94% yield, 86% de, 99% ee
19h: $R^1 = R^3 = \text{Ph}$, $\text{Ar} = p\text{-Tol}$, $R^2 = \text{Et}$: 90% yield, 88% de, 99% ee
19i: $R^1 = R^3 = \text{Ph}$, $\text{Ar} = p\text{-MeOC}_6\text{H}_4$, $R^2 = \text{Et}$: 88% yield, 90% de, 99% ee
19j: $R^1 = \text{Ar} = \text{Ph}$, $R^2 = \text{Et}$, $R^3 = o\text{-FC}_6\text{H}_4$: 94% yield, 82% de, 99% ee
19k: $R^1 = \text{Ar} = \text{Ph}$, $R^2 = \text{Et}$, $R^3 = m\text{-FC}_6\text{H}_4$: 91% yield, 84% de, 99% ee
19l: $R^1 = \text{Ar} = \text{Ph}$, $R^2 = \text{Et}$, $R^3 = p\text{-FC}_6\text{H}_4$: 90% yield, 76% de, 99% ee
19m: $R^1 = \text{Ar} = \text{Ph}$, $R^2 = \text{Et}$, $R^3 = o\text{-ClC}_6\text{H}_4$: 93% yield, 78% de, 99% ee
19n: $R^1 = \text{Ar} = \text{Ph}$, $R^2 = \text{Et}$, $R^3 = p\text{-ClC}_6\text{H}_4$: 96% yield, 78% de, 99% ee
19o: $R^1 = \text{Ar} = \text{Ph}$, $R^2 = \text{Et}$, $R^3 = m\text{-Tol}$: 75% yield, 88% de, 99% ee
19p: $R^1 = \text{Ar} = \text{Ph}$, $R^2 = \text{Et}$, $R^3 = p\text{-Tol}$: 91% yield, 86% de, 99% ee
19q: $R^1 = \text{Ar} = \text{Ph}$, $R^2 = \text{Et}$, $R^3 = p\text{-MeOC}_6\text{H}_4$: 59% yield, 86% de, 99% ee
19r: $R^1 = \text{Ar} = \text{Ph}$, $R^2 = \text{Et}$, $R^3 = 3\text{-thienyl}$: 90% yield, 88% de, 97% ee
19s: $R^1 = \text{Ar} = \text{Ph}$, $R^2 = \text{Et}$, $R^3 = n\text{-Bu}$: 73% yield, 78% de, 99% ee
19t: $R^1 = R^3 = \text{Ar} = \text{Ph}$, $R^2 = \text{Me}$: 88% yield, 88% de, 99% ee
19u: $R^1 = R^3 = \text{Ar} = \text{Ph}$, $R^2 = i\text{-Pr}$: 82% yield, 72% de, 98% ee
19v: $R^1 = R^3 = \text{Ar} = \text{Ph}$, $R^2 = t\text{-Bu}$: 61% yield, 38% de, 99% ee

proposed *Si* face attack:

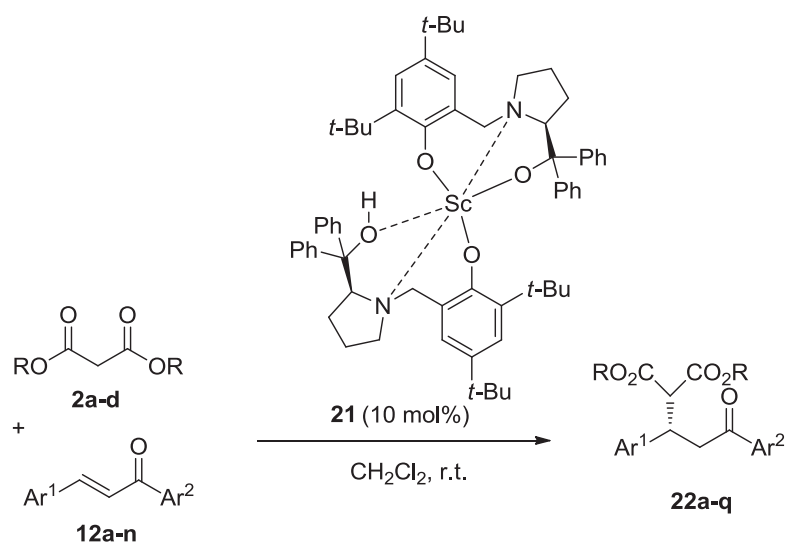


Scheme 6. Scandium-catalyzed Michael addition of malonates to enynes [17].

carbon–heteroatom bonds with high levels of stereoselection [5p–q,6a–c]. The general structure of REMB complexes is depicted in Fig. 1.

Despite their exceptional performance, there are several challenges that have prevented the widespread practical application

of REMB catalysts, such as their sensitivity to air and trace amounts of moisture. In 2014, Pericas, Schelter, and Walsh developed novel air- and water-tolerant rare earth guanidinium BINOLate complexes as practical REMB precatalysts [20]. Indeed, incorporation of hydrogen-bonded guanidinium cations in the secondary



- 22a:** Ar¹ = Ar² = Ph, R = Et: 95% yield, 78% ee
22b: Ar¹ = Ar² = Ph, R = Me: 85% yield, 70% ee
22c: Ar¹ = Ar² = Ph, R = *i*-Pr: 95% yield, 90% ee
22d: Ar¹ = Ar² = Ph, R = *t*-Bu: 93% yield, 83% ee
22e: Ar¹ = *p*-MeOC₆H₄, Ar² = Ph, R = *i*-Pr: 92% yield, 83% ee
22f: Ar¹ = *p*-ClC₆H₄, Ar² = Ph, R = *i*-Pr: 99% yield, 89% ee
22g: Ar¹ = *p*-BrC₆H₄, Ar² = Ph, R = *i*-Pr: 99% yield, 87% ee
22h: Ar¹ = *p*-F₃CC₆H₄, Ar² = Ph, R = *i*-Pr: 90% yield, 64% ee
22i: Ar¹ = Ph, Ar² = *p*-MeOC₆H₄, R = *i*-Pr: 82% yield, 88% ee
22j: Ar¹ = Ph, Ar² = 2-Naph, R = *i*-Pr: 90% yield, 88% ee
22k: Ar¹ = Ph, Ar² = *p*-FC₆H₄, R = *i*-Pr: 95% yield, 86% ee
22l: Ar¹ = Ph, Ar² = *p*-ClC₆H₄, R = *i*-Pr: 97% yield, 84% ee
22m: Ar¹ = Ph, Ar² = *p*-O₂NC₆H₄, R = *i*-Pr: 99% yield, 77% ee
22n: Ar¹ = Ph, Ar² = *o*-ClC₆H₄, R = *i*-Pr: 86% yield, 81% ee
22o: Ar¹ = Ph, Ar² = *o*-MeOC₆H₄, R = *i*-Pr: 80% yield, 86% ee
22p: Ar¹ = 1-furyl, Ar² = Ph, R = *i*-Pr: 97% yield, 89% ee
22q: Ar¹ = 1-thienyl, Ar² = Ph, R = *i*-Pr: 95% yield, 82% ee

Scheme 7. Scandium-catalyzed Michael addition of malonates to chalcones [18].

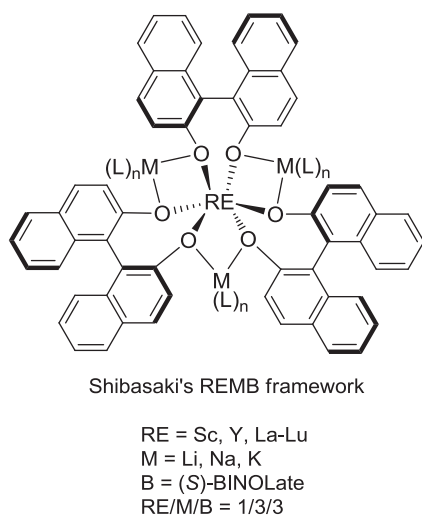
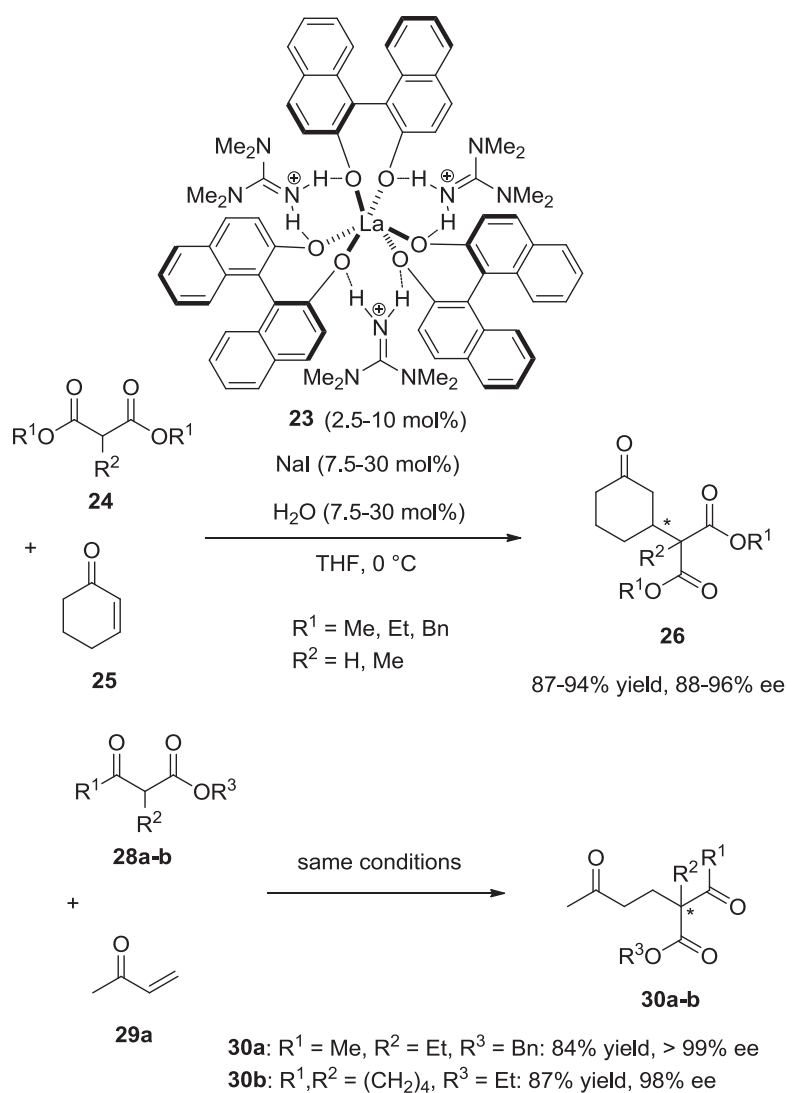
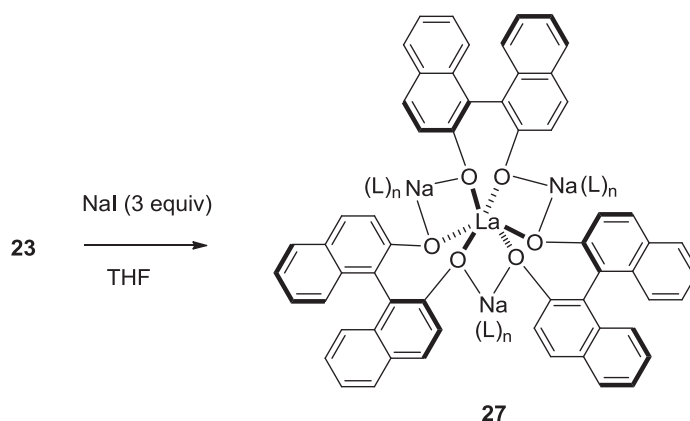


Fig. 1. Structure of heterobimetallic Shibasaki's REMB complexes.

coordination sphere of the complex led to unique properties, notably, improved stability toward moisture in solution and in the solid state. These properties were exploited to develop straightforward, high-yielding, and open-air syntheses of crystalline, nonhygroscopic complexes, such as **23**, that could be used as precatalysts for Shibasaki's REMB frameworks. As shown in **Scheme 8**, when precatalyst **23** was applied to promote the asymmetric Michael addition of 1,3-dicarbonyl compounds, such as malonates **24**, to cyclohexenone **25**, it afforded the corresponding chiral cyclohexanone derivatives **26** in excellent yields and enantioselectivities of 87–94% and 88–96% ee, respectively. The reaction was performed in THF at 0 °C in the presence of catalytic amounts of water as additive and NaI to generate the active heterobimetallic Shibasaki-type REMB catalyst **27**. The success of this novel precatalyst system was attributed to the use of NaI, which cleanly generated the corresponding active complex **27** through cation-exchange while producing an innocent guanidinium iodide spectator ion (**Scheme 8**). The scope of the methodology was extended to other Michael donors and acceptors, such as cyclic as well as acyclic β -ketoesters **28a–b** and methyl vinyl ketone **29a**, which reacted smoothly to give the corresponding Michael products **30a–b** in high yields (84–87%) and remarkable enantioselectivities



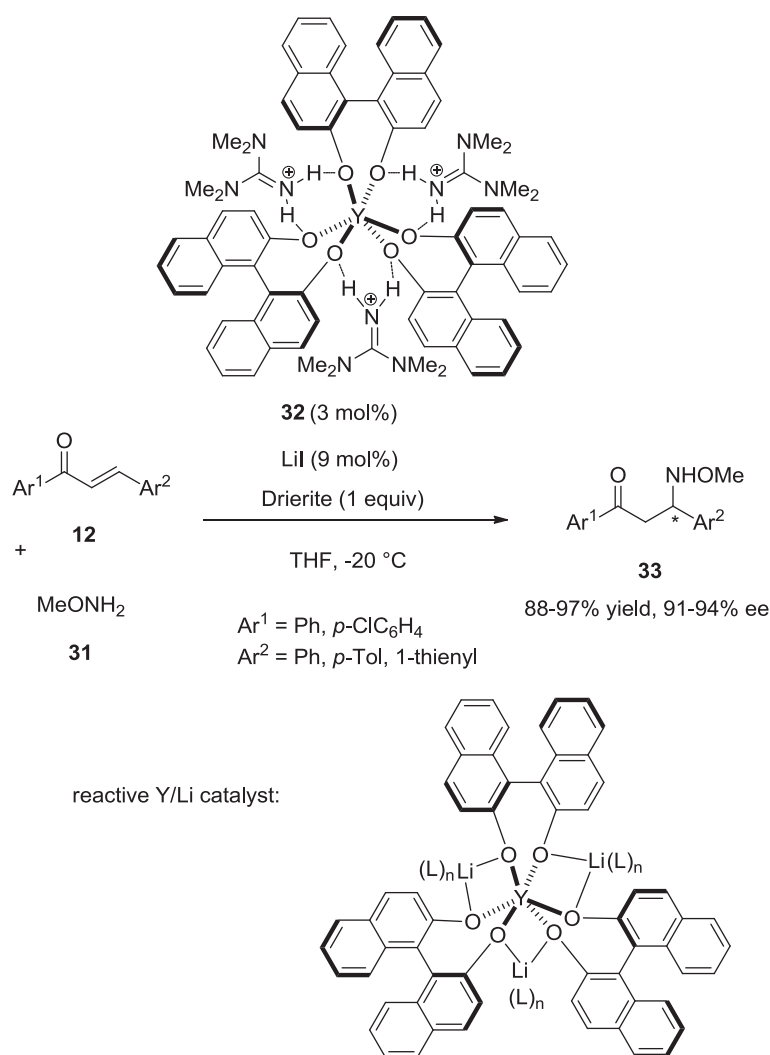
in situ preparation of reactive REMB La/Na catalyst **27**:



Scheme 8. Michael additions of 1,3-dicarbonyl compounds to α,β -unsaturated ketones using lanthanum precatalyst **23** [20].

(98→99% ee). While classical REMB catalysts can be stored at room temperature for extended periods of time under a dry N₂ atmosphere with no significant loss in catalytic activity, the novel rare earth guanidinium BINOLate complexes, such as **23**, could be stored in vials exposed to open air for six months, and then employed in the same Michael reactions. Under these conditions,

this precatalyst maintained excellent catalytic activity, whereas the performance of classical REMB complexes was significantly reduced due to the decomposition associated with prolonged exposure to ambient atmosphere. These experiments supported the tolerance of precatalyst **23** to benchtop conditions, and highlighted its suitability as robust precatalyst.



Scheme 9. Aza-Michael addition of methylhydroxylamine to chalcones using yttrium precatalyst **32** [20].

A key attribute of the REMB framework is the diversity observed in the catalytic reactions upon changing RE and M combinations. To establish that precatalyst **23** was amenable to different RE/M combinations, the asymmetric aza-Michael addition of methylhydroxylamine **31** to chalcones **12** was investigated [20]. Indeed, the use of yttrium complex **32** as precatalyst of the corresponding heterobimetallic Y/Li/BINOL active catalyst at only 3 mol% of catalyst loading in these reactions allowed the corresponding aza-Michael products **33** to be obtained in both excellent yields and enantioselectivities of 88–97% and 91–94% ee, respectively (Scheme 9).

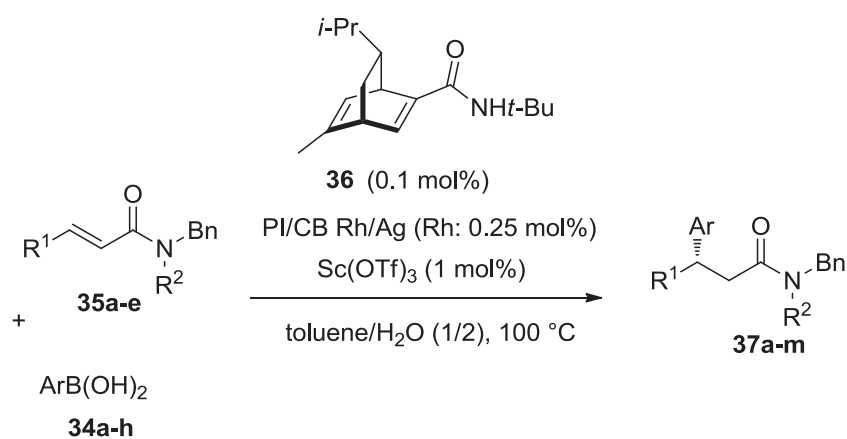
In another context, Kobayashi et al. recently developed cooperative catalysts consisting of a combination of chiral Rh/Ag nanoparticles immobilized on a nanocomposite of polystyrene-based copolymers with cross-linking moieties and carbon black (PI/CB catalyst), with Sc(OTf)₃ to be applied to asymmetric Michael additions of arylboronic acids **34a–h** to challenging because low reactive α,β -unsaturated amides **35a–e** [21]. The chirality of the catalyst system arose from chiral ligand **36** used at catalyst loading as low as 0.1 mol%. As shown in Scheme 10, the process afforded a series of almost enantiopure amide products **37a–m** (98–>99% ee) in moderate to high yields (56–93%). Although the role of the different metals used in the process was not clear, it was demonstrated that Sc(OTf)₃ enhanced significantly the catalytic performance through a synergistic effect. Moreover, Sc(OTf)₃ lowered the LUMO level of the amide substrate to accelerate the

carbon–carbon bond-forming step. As shown in Scheme 10, in addition to methyl-substituted substrate **35a** (R¹ = Me, R² = H) that afforded products **37a–h** in 77–93% yield and 98–>99% ee, several *N*-benzyl unsaturated amides, including aliphatic substrate (R¹ = *n*-Pent), aromatic substrate (R¹ = *p*-Tol), sterically bulky isopropyl group-substituted substrate (R¹ = *i*-Pr), and cyclic substrate with a six-membered ring (R¹, R² = (CH₂)₂), were converted into the corresponding Michael products **37i–m** in good yields (56–88%) with outstanding enantioselectivity (99% ee). Furthermore, arylboronic acids with either electron-donating or electron-withdrawing groups were all tolerated. The catalyst could be recovered and reused by a simple procedure without significantly loss of activity. The utility of this methodology was demonstrated by its application to the formal synthesis of a pharmacologically important compound, (–)-paroxetine, starting from product **37m** (Scheme 10).

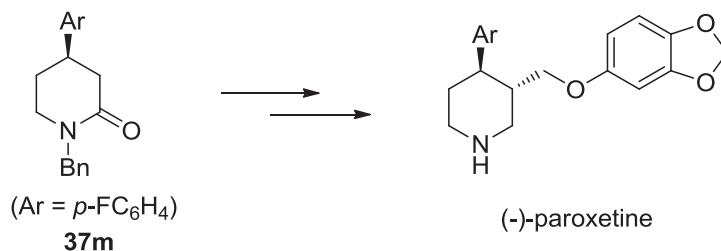
3. Enantioselective lanthanide-catalyzed cycloaddition reactions

3.1. 1,3-Dipolar cycloadditions

Cycloaddition reactions constitute important tools for the assembly of complex molecular structures [22]. Among them, the 1,3-dipolar cycloaddition [23] of a dipolarophile with a



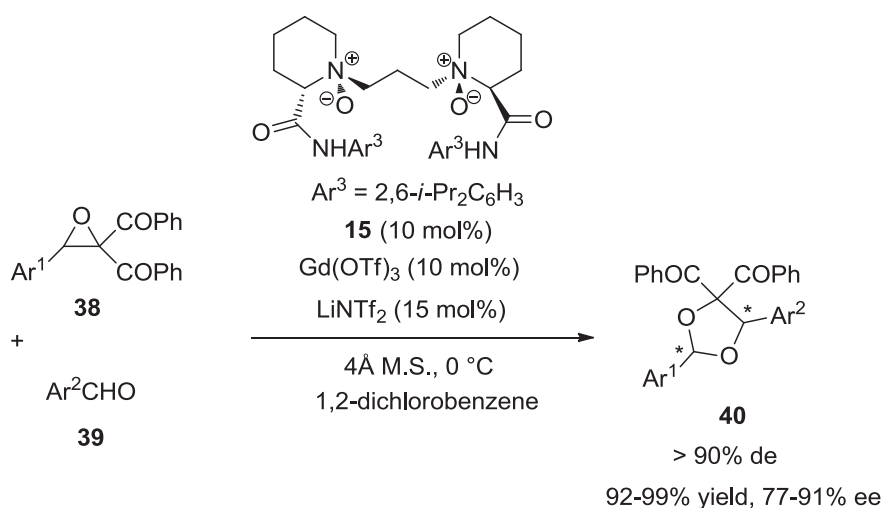
- 37a:** R¹ = Me, R² = H, Ar = Ph: 93% yield, 98% ee
37b: R¹ = Me, R² = H, Ar = *o*-MeOC₆H₄: 88% yield, > 99% ee
37c: R¹ = Me, R² = H, Ar = *m*-MeOC₆H₄: 85% yield, 98% ee
37d: R¹ = Me, R² = H, Ar = *p*-MeOC₆H₄: 90% yield, 98% ee
37e: R¹ = Me, R² = H, Ar = *m*-Tol: 85% yield, 99% ee
37f: R¹ = Me, R² = H, Ar = *p*-Tol: 84% yield, 98% ee
37g: R¹ = Me, R² = H, Ar = *p*-ClC₆H₄: 77% yield, 99% ee
37h: R¹ = Me, R² = H, Ar = *p*-FC₆H₄: 81% yield, 98% ee
37i: R¹ = *n*-Pent, R² = H, Ar = Ph: 88% yield, 99% ee
37j: R¹ = *p*-Tol, R² = H, Ar = Ph: 69% yield, 99% ee
37k: R¹ = *i*-Pr, R² = H, Ar = Ph: 72% yield, 99% ee
37l: R¹, R² = (CH₂)₂, Ar = Ph: 56% yield, 99% ee
37m: R¹, R² = (CH₂)₂, Ar = *p*-FC₆H₄: 72% yield, 99% ee



Scheme 10. Michael addition of arylboronic acids to α,β -unsaturated amides cooperatively catalyzed by Sc(OTf)₃ and immobilized chiral Rh/Ag nanoparticles [21].

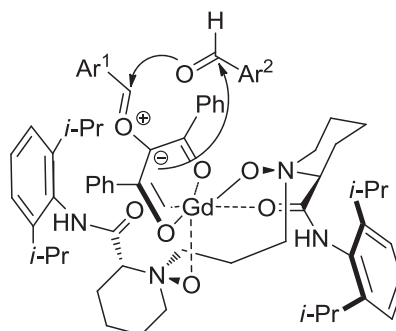
1,3-dipolar compound allows the production of important five-membered heterocycles [24]. Early in 1997, Jørgensen et al. reported asymmetric ytterbium-catalyzed 1,3-dipolar cycloadditions performed in the presence of a Pybox ligand, providing cycloadducts in enantioselectivities of up to 73% ee [25]. Ever since, other lanthanide chiral catalysts have been employed to promote various asymmetric [3+2] cycloadditions. As a recent example, Feng et al. developed a novel and efficient *N,N'*-dioxide-gadolinium complex, in situ generated from the corresponding ligand **15** and Gd(OTf)₃, that was employed to catalyze highly diastereo- and enantioselective 1,3-dipolar cycloadditions of carbonyl ylides derived from aryl oxiranyl diketones **38** with aromatic aldehydes **39** [26]. The process evolved through carbon-carbon bond cleavage of the epoxides, leading to the corresponding chiral 1,3-dioxolanes **40** as almost single diastereomers (>90% de) in very high yields (92–99%) and good to high enantioselectivities (77–91% ee), as shown in Scheme 11. The reaction was performed in 1,2-dichlorobenzene at 0 °C in the presence of 15 mol% of LiNTf₂ as additive. The reaction conditions were compatible to a number of

epoxides and aromatic aldehydes. Epoxides bearing electron-donating and electron-withdrawing groups at *meta*- and *para*-positions of the phenyl ring of Ar¹ provided the corresponding products in 80–90% ee, while the reaction of a 1-naphthyl-substituted epoxide gave the lowest enantioselectivity of 77% ee. 2-Naphthyl-, 3-furyl-, and 3-thienyl-substituted substrates were also suitable in the reaction, delivering the corresponding products in 87, 89, and 82% ee, respectively. Moreover, a range of aromatic aldehydes bearing electron-withdrawing or electron-donating groups at the *ortho*-, *para*-, or *meta*-positions of the phenyl ring of Ar² were compatible, giving enantioselectivities of up to 86% ee. Notably, heteroaromatic-substituted aldehydes also reacted smoothly to give the corresponding cycloadducts in 86–91% ee. The transition state depicted in Scheme 11 shows that Gd(III) coordinated to all the oxygen atoms of ligand **15** through a tetradentate manner. The catalyst also coordinated with the oxygen atoms of the C=O groups in epoxide **38**, that led to the formation of the corresponding carbonyl ylide, and an hexacoordinated Gd(III)-derived intermediate was generated. The oxygen atom of aldehyde **39**



$\text{Ar}^1 = \text{Ph}, m\text{-Tol}, m\text{-MeOC}_6\text{H}_4, m\text{-PhOC}_6\text{H}_4, p\text{-Tol}, m\text{-ClC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4,$
 $m\text{-BrC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, 1\text{-Naph}, 2\text{-Naph}, 3\text{-furyl}, 3\text{-thienyl}$
 $\text{Ar}^2 = \text{Ph}, m\text{-Tol}, p\text{-Tol}, o\text{-FC}_6\text{H}_4, m\text{-FC}_6\text{H}_4, p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, 2\text{-furyl},$
 $3\text{-furyl}, 2\text{-thienyl}, 3\text{-thienyl}$

proposed transition state:



Scheme 11. Gadolinium-catalyzed 1,3-dipolar cycloaddition of aromatic aldehydes with epoxides [26].

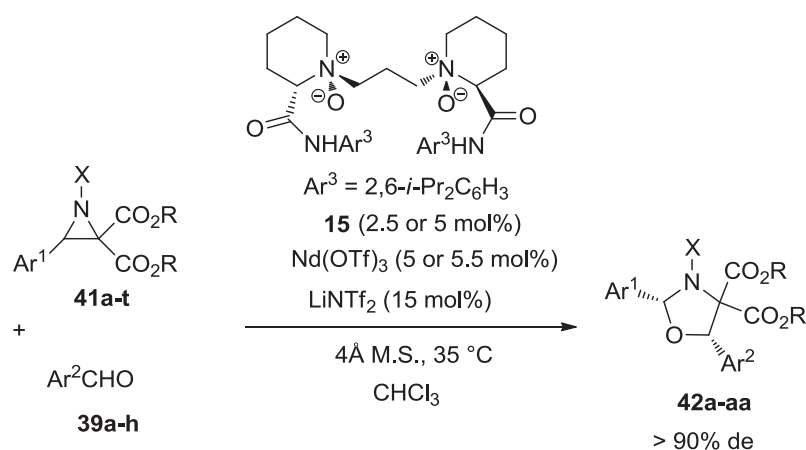
attacked the *re*-face of the carbonyl ylide, because its *Si*-face was shielded by the neighboring 2,6-diisopropylphenyl group of the ligand. Then, a ring closure occurred to afford final product **40**.

In 2016, a combination of the same *N,N'*-dioxide ligand **15** with $\text{Nd}(\text{OTf})_3$ in the presence of LiNTf_2 as additive was employed to promote enantioselective 1,3-dipolar cycloadditions of aromatic aldehydes **39a–h** with aziridines **41a–t** [27]. Evolving through carbon–carbon bond cleavage, the process allowed the efficient production of the corresponding chiral *cis*-1,3-oxazolidines **42a–aa** in good to high enantioselectivities (72–95% ee) and moderate to excellent yields (38–98%), as shown in Scheme 12. The presence of 15 mol% of LiNTf_2 was beneficial for both the reactivity and enantioselectivity of the process. The ester moieties of the aziridine (R), the methyl group had less influence on the outcome than the ethyl group, while the isopropyl group was detrimental to both the reactivity and enantioselectivity (62–68% yield and 90–91% ee for products **42a–b** vs 40% yield and 72% ee for product **42c**). Various benzenesulfonyl motifs (X) were tolerated in aziridines but lower yields (6–54%) and enantioselectivities (62–76% ee) were obtained for products **42g–h** bearing 2-methyl and 2-nitro substituents as a result of the steric hindrance at the 2-position. Noteworthy, methanesulfonyl-substituted product **42i** and 2-trimethylsilylethanesulfonyl-substituted product **42j** were formed in 66–77% yields and 93–95% ee. Furthermore, a variety of aryl aziridines with electron-withdrawing substituents on the phenyl ring of Ar^1 group provided the corresponding cycloadducts **42k–**

q in 66–98% yields and 87–94% ee. The Ar^1 group of the aziridine could also be replaced by biphenyl or 2-naphthyl groups since the corresponding products **42r–s** were obtained in good to high yields (70–94%) and high enantioselectivity (93% ee). On the other hand, alkyl-substituted aziridines were demonstrated to be inert. Concerning the aromatic aldehyde partners **39a–h**, electron-withdrawing- and electron-donating-substituted ones led to the corresponding cycloadducts **42t–y** in moderate to high yields (38–73%) and good enantioselectivities (84–94% ee). Heteroaromatic aldehydes were also compatible, giving products **42z–aa** in 84–93% yields and 91–94% ee.

The catalytic cycle depicted in Scheme 13 is based on a dual Lewis acids relay catalysis [27]. Firstly, with the assistance of LiNTf_2 , the carbon–carbon bond of the aziridine was cleaved to form a dipolar intermediate **E**. The latter was subsequently caught by the chiral $\text{Nd}(\text{III})/\mathbf{15}$ complex due to the strong bidentate coordination of the two ester groups to the metal center. A concerted [3+2] cycloaddition then underwent enantioselectively to give final product **42** with the regeneration of the catalyst.

In 2013, Suga et al. reported asymmetric 1,3-dipolar cycloadditions of carbonyl ylides generated from *N*-diazoacetyl lactams **43a–c** with 3-(2-alkenyl)-2-oxazolidinones **44a–f** catalyzed by chiral lanthanide triflates derived from Pybox ligand **45** [28]. The process was performed in the presence of 2 mol% of $\text{Rh}(\text{OAc})_4$ that promoted the generation of carbonyl ylide **46** from *N*-diazoacetyl lactam **43** (mechanism in Scheme 14). By using $\text{La}(\text{OTf})_3$ as



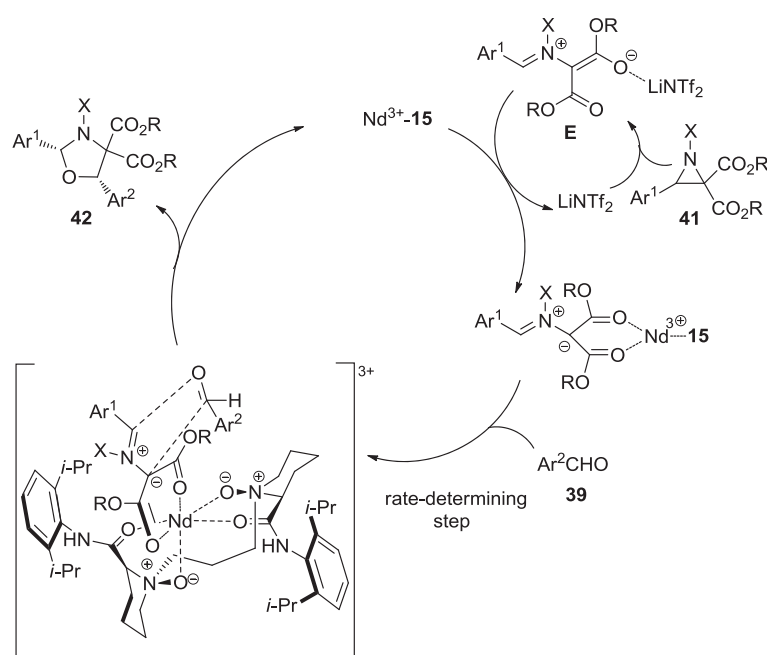
- 42a:** X = SO₂*p*-Tol, R = Et, Ar¹ = Ar² = Ph: 68% yield, 91% ee
42b: X = SO₂*p*-Tol, R = Me, Ar¹ = Ar² = Ph: 62% yield, 90% ee
42c: X = SO₂*p*-Tol, R = *i*-Pr, Ar¹ = Ar² = Ph: 40% yield, 72% ee
42d: X = SO₂*p*-ClC₆H₄, R = Et, Ar¹ = Ar² = Ph: 74% yield, 89% ee
42e: X = SO₂Ph, R = Et, Ar¹ = Ar² = Ph: 70% yield, 90% ee
42f: X = SO₂*p*-MeOC₆H₄, R = Et, Ar¹ = Ar² = Ph: 60% yield, 90% ee
42g: X = SO₂*o*-Tol, R = Et, Ar¹ = Ar² = Ph: 54% yield, 76% ee
42h: X = SO₂*o*-O₂NC₆H₄, R = Et, Ar¹ = Ar² = Ph: 6% yield, 62% ee
42i: X = SO₂Me, R = Et, Ar¹ = Ar² = Ph: 77% yield, 95% ee
42j: X = SO₂(CH₂)₂TMS, R = Et, Ar¹ = Ar² = Ph: 66% yield, 93% ee
42k: X = SO₂Me, R = Et, Ar¹ = *p*-ClC₆H₄, Ar² = Ph: 80% yield, 91% ee
42l: X = SO₂Me, R = Et, Ar¹ = *m*-ClC₆H₄, Ar² = Ph: 78% yield, 92% ee
42m: X = SO₂Me, R = Et, Ar¹ = *o*-ClC₆H₄, Ar² = Ph: 71% yield, 88% ee
42n: X = SO₂Me, R = Et, Ar¹ = *p*-BrC₆H₄, Ar² = Ph: 70% yield, 93% ee
42o: X = SO₂Me, R = Et, Ar¹ = *p*-FC₆H₄, Ar² = Ph: 66% yield, 94% ee
42p: X = SO₂Me, R = Et, Ar¹ = *p*-F₃CC₆H₄, Ar² = Ph: 98% yield, 91% ee
42q: X = SO₂Me, R = Et, Ar¹ = *p*-O₂NC₆H₄, Ar² = Ph: 84% yield, 87% ee
42r: X = SO₂Me, R = Et, Ar¹ = *p*-PhC₆H₄, Ar² = Ph: 70% yield, 93% ee
42s: X = SO₂Me, R = Et, Ar¹ = 2-Naph, Ar² = Ph: 94% yield, 93% ee
42t: X = SO₂Me, R = Et, Ar¹ = Ph, Ar² = *p*-ClC₆H₄: 70% yield, 90% ee
42u: X = SO₂Me, R = Et, Ar¹ = Ar² = *m*-ClC₆H₄: 38% yield, 89% ee
42v: X = SO₂Me, R = Et, Ar¹ = *p*-ClC₆H₄, Ar² = *p*-Tol: 51% yield, 84% ee
42w: X = SO₂Me, R = Et, Ar¹ = *p*-ClC₆H₄, Ar² = *m*-Tol: 73% yield, 94% ee
42x: X = SO₂Me, R = Et, Ar¹ = Ar² = *m*-Tol: 51% yield, 92% ee
42y: X = SO₂Me, R = Et, Ar¹ = *p*-ClC₆H₄, Ar² = *m*-MeOC₆H₄: 70% yield, 93% ee
42z: X = SO₂Me, R = Et, Ar¹ = *p*-ClC₆H₄, Ar² = 3-thienyl: 84% yield, 91% ee
42aa: X = SO₂Me, R = Et, Ar¹ = *p*-ClC₆H₄, Ar² = 2-furyl: 93% yield, 94% ee

Scheme 12. Neodymium-catalyzed 1,3-dipolar cycloaddition of aromatic aldehydes with aziridines [27].

precatalyst, several alkyl-substituted 3-(2-alkenoyl)-2-oxazolidinones **44a–c** (R ≠ H) reacted with *N*-diazocetyl lactams **43a–b** possessing six- and seven-membered rings to give the corresponding epoxy-bridged quinolizidines and 1-azabicyclo[5.4.0]undecanes **47a–f** in good yields (62–78%) and enantioselectivities (84–88% ee) with *exo/endo* ratios of 85:15 to 93:7 (Scheme 14). In the reaction of non-substituted 3-(2-alkenoyl)-2-oxazolidinone **44d** (R = H) with *N*-diazocetyl lactams **43a–b** possessing six- and seven-membered rings, the best results were achieved by using Lu(OTf)₃ or Tm(OTf)₃ instead of La(OTf)₃ as precatalyst at 10 °C. Indeed, the lutetium- and thulium-catalyzed reaction of **44d** with *N*-diazocetyl lactams **43a–b** yielded the corresponding cycloadducts **47g–h** in moderate yields (53–55%), good enantioselectivities (85–87% ee), and *exo/endo* ratios of 79:21 to 93:7 (Scheme 14).

Moreover, *N*-diazocetyl lactam **43c** possessing a five-membered ring (n = 0) reacted with (substituted) 3-(2-alkenoyl)-2-oxazolidinones **44a–d** in the presence of La(OTf)₃ at variable temperatures (–20, –10, 0 or 10 °C) to give the corresponding epoxy-bridged indolizidines **47i–l** in moderate to quantitative yields (44–100%), good to excellent enantioselectivities (81–95% ee), and with *exo/endo* ratios of 75:25 to 99:1 (Scheme 14). As synthetic utility of this methodology, indolizidine **47i** could be further converted into natural indolizidine alkaloid (+)-tashiromine.

In 2015, the same lutetium catalyst derived from Pybox ligand **45** was applied to the asymmetric 1,3-dipolar cycloaddition of *N*-methylindoles **48a–d** with carbonyl ylides derived from diazodiketones **49a–i** and diazoketone **49j** [29]. In this case, the reaction was performed in toluene at 10 °C, and yielded the corresponding



Scheme 13. Plausible catalytic cycle for 1,3-dipolar cycloaddition of aromatic aldehydes with aziridines (Scheme 12) [27].

chiral cycloadducts *exo*-**50a–m** and *endo*-**50a–m** in moderate to good yields of up to 85%, enantioselectivities of up to >98% ee, and *exo/endo* ratios of up to >99:1. As shown in Scheme 15, the best results concerning the reaction of diazodiketones **49a–i** were obtained when they exhibited an aryl substituent ($R^2 = \text{aryl}$) since the corresponding products **50a–f,i–l** were formed in 63–85% yields, 83–>98% ee, and with *exo/endo* ratios of 65:35 to 94:6. Indeed, alkyl-substituted diazodiketones **49d–e** ($R^2 = \text{Me}, i\text{-Pr}$) gave lower results since the corresponding products **50g–hw** were obtained in 39–56% yields, 52–68% ee, and *exo/endo* ratios of 57:43 to 71:29. In addition, the scope of the process was extended to diazoketoester **49j** which reacted to deliver product **50m** in 82% yield, relatively good enantioselectivity of 79% ee albeit with an outstanding *exo/endo* ratio of >99:1.

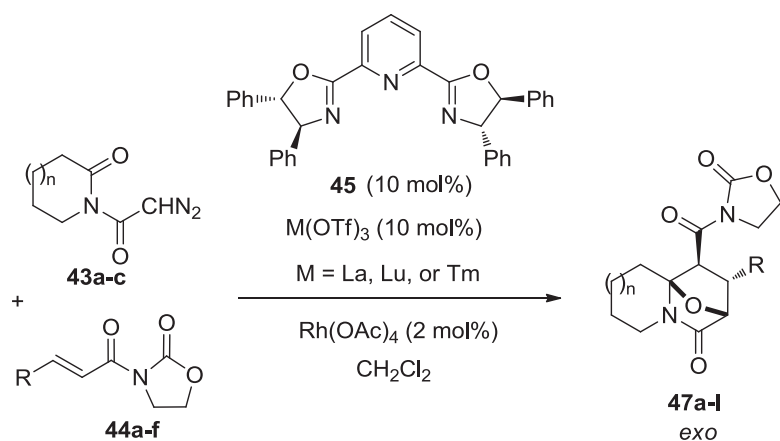
3.2. (Hetero)-Diels–Alder cycloadditions

The asymmetric (hetero)-Diels–Alder reaction is one of the most efficient synthetic methodologies for the regio- and stereoselective construction of chiral six-membered (hetero)cycles [30]. As previously mentioned in the Introduction, Danishefsky et al. pioneered the use of chiral lanthanide complexes as catalysts in organic reactions through the development of asymmetric europium-catalyzed hetero-Diels–Alder reactions between aldehydes and siloxydienes, providing the corresponding cycloadducts with enantioselectivities of up to 58% ee by using only 1 mol% of catalyst loading [2]. Later, better enantioselectivities of up to 98% ee were independently reported by Kobayashi, Nakagawa, and Marko in Diels–Alder reactions promoted by chiral ytterbium catalysts derived from BINOL [31]. Ever since, other chiral lanthanide catalysts have been applied to promote asymmetric Diels–Alder cycloadditions. As a recent example, Nishida et al. reported asymmetric Diels–Alder cycloadditions of 3-[1-(silyloxy)vinyl]indole **51** with *N*-acyloxazolidinones **44a–k** promoted by a novel chiral holmium catalyst in situ generated from $\text{Ho}(\text{NTf}_2)_3$ and chiral bis-thiourea ligand **52** [32]. The reaction was performed in dichloromethane in the presence of 10 mol% of DBU that was supposed to deprotonate the NH of the ligand. It led to a series of chiral highly functionalized hydrocarbazoles **53a–k** as single *exo*-diastereomers

in uniformly high yields (86–99%) and good to high enantioselectivities (75–94% ee). As shown in Scheme 16, the scope of *N*-acyloxazolidinones **44a–k** was wide since various functions, such as thioester, ester, acetyl, cyano, and trifluoromethyl groups, were tolerated as R substituents, leading to the corresponding products **53a–e** in 78–94% ee. Moreover, alkyl-substituted dienophiles delivered products **53g–j** in $\geq 90\%$ ee while phenyl-substituted substrate **44f** was associated with a slight decrease in enantioselectivity (75% ee for product **53f**). The synthetic utility of this novel methodology was demonstrated in a total synthesis of natural alkaloid (–)-minovincine (Scheme 16) [33].

The REMB system is highly tunable, and simple changes in the identity of RE (and M) retain the catalyst scaffolding, but result in dramatic differences in reactivity and enantioselectivity. In 2013, Schelter et al. reported the first heterobimetallic BINOLate complexes incorporating uranium and lithium [34]. Indeed, complex $[\text{Li}_3(\text{THF})_5][(\text{6,6'}\text{-Br}_2\text{-BINOLate})_3\text{U}-(\text{6,6'}\text{-Br}_2\text{-H}_1\text{-BINOL})]$ **54** was readily prepared by treatment of UCl_4 in THF at room temperature with 4 equivalents of $\text{Li}_2[(S)\text{-6,6'}\text{-Br}_2\text{-BINOLate}]$. This novel uranium(IV)//Li/BINOLate heterobimetallic complex was further investigated as catalyst in the asymmetric Diels–Alder cycloaddition of cyclopentadiene **55** with *N*-acyloxazolidinone **44k** to give the corresponding cycloadduct **56** (Scheme 17). The reaction was performed in toluene at -20°C , providing product **56** in good yield (78%), high *endo/exo* ratio (92:8), and moderate enantioselectivity of 63% ee. This result represented the highest enantioselectivity obtained by using a uranium-based catalyst. Moreover, the product was obtained free of radioactivity trace by using a simple workup procedure, demonstrating the easy and safe application of uranium in catalytic reactions.

In 2014, Wang et al. developed novel asymmetric ytterbium-catalyzed oxa-Diels–Alder cycloadditions of isatins **57a–j** with α, β -unsaturated methyl ketones **58a–j** to give the corresponding chiral spirooxindole tetrahydropyranones **59a–s** [35]. As shown in Scheme 18, the cycloaddition was performed in dichloromethane at room temperature in the presence of an ytterbium chiral catalyst in situ generated from $\text{Yb}(\text{OTf})_3$ and chiral amide ligand **60**. It involved the combination of enamine catalysis with metal Lewis acid catalysis, as illustrated in the proposed transition state



with M = La at 10 °C:

47a: R = Me, n = 1: 78% yield, *exo/endo* = 85:15, 87% ee (*exo*)

47b: R = Et, n = 1: 68% yield, *exo/endo* = 87:13, 86% ee (*exo*)

47c: R = *n*-Pr, n = 1: 62% yield, *exo/endo* = 87:13, 84% ee (*exo*)

47d: R = Me, n = 2: 76% yield, *exo/endo* = 93:7, 88% ee (*exo*)

47e: R = Et, n = 2: 75% yield, *exo/endo* = 91:9, 87% ee (*exo*)

47f: R = *n*-Pr, n = 2: 64% yield, *exo/endo* = 83:17, 84% ee (*exo*)

with M = Lu at 10 °C:

47g: R = H, n = 1: 55% yield, *exo/endo* = 79:21, 87% ee (*exo*)

with M = Tm at 10 °C:

47h: R = H, n = 2: 53% yield, *exo/endo* = 93:7, 85% ee (*exo*)

with M = La at 10, -20, 0 or -10 °C:

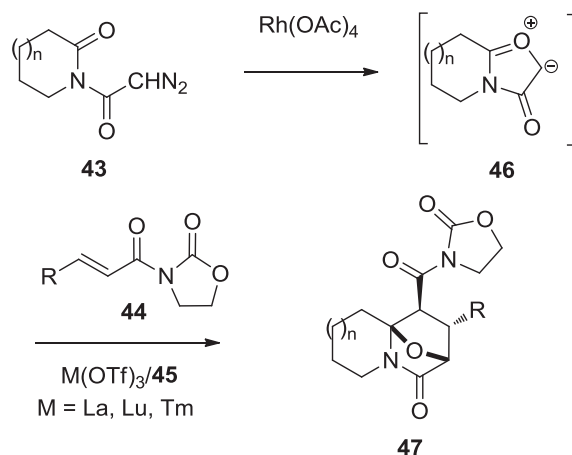
47i: R = H, n = 0: 100% yield, *exo/endo* = 92:8, 87% ee (at 10 °C)

47j: R = Me, n = 0: 100% yield, *exo/endo* = 75:25, 95% ee (at -20 °C)

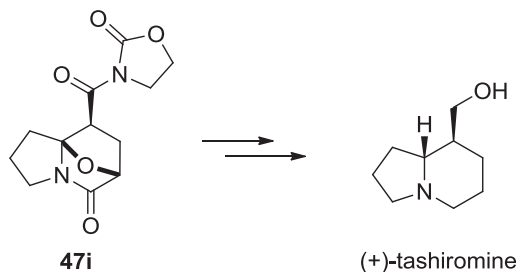
47k: R = *i*-Pr, n = 0: 44% yield, *exo/endo* = 95:5, 93% ee (at 0 °C)

47l: R = OAc, n = 0: 60% yield, *exo/endo* = 99:1, 81% ee (at -10 °C)

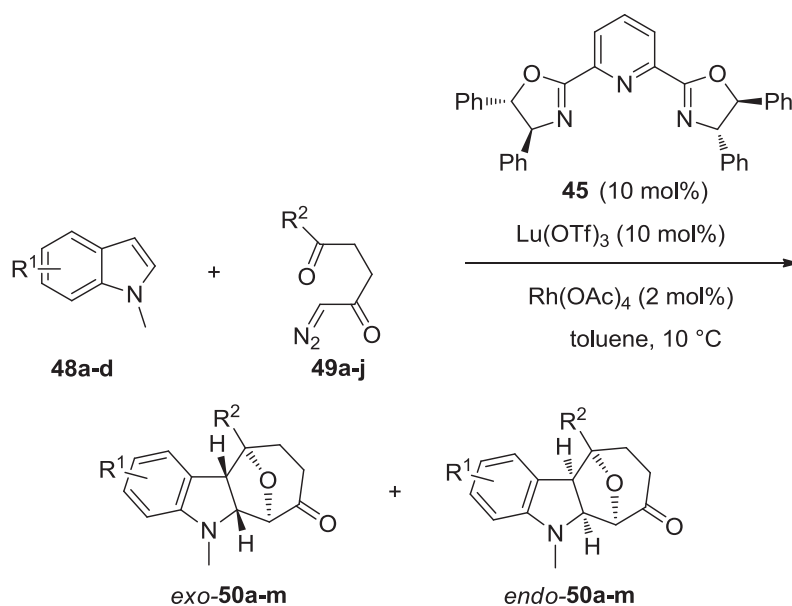
proposed mechanism:



synthesis of tashiromine:



Scheme 14. Lanthanum-, lutetium-, and thulium-catalyzed 1,3-dipolar cycloaddition of 3-(2-alkenyl)-2-oxazolidinones with *N*-diazoacetyl lactams [28].



- 50a:** $R^1 = \text{H}$, $R^2 = \text{Ph}$: 77% yield, *exo/endo* = 78:22, 90% ee (*exo*)
50b: $R^1 = 5\text{-Br}$, $R^2 = \text{Ph}$: 76% yield, *exo/endo* = 88:12, 96% ee (*exo*)
50c: $R^1 = 5\text{-OMe}$, $R^2 = \text{Ph}$: 77% yield, *exo/endo* = 71:29, 88% ee (*exo*)
50d: $R^1 = 6\text{-OMe}$, $R^2 = \text{Ph}$: 65% yield, *exo/endo* = 71:29, 92% ee (*exo*)
50e: $R^1 = \text{H}$, $R^2 = p\text{-Tol}$: 85% yield, *exo/endo* = 65:35, 83% ee (*exo*)
50f: $R^1 = \text{H}$, $R^2 = p\text{-BrC}_6\text{H}_4$: 73% yield, *exo/endo* = 72:28, 84% ee (*exo*)
50g: $R^1 = \text{H}$, $R^2 = \text{Me}$: 56% yield, *exo/endo* = 57:43, 52% ee (*exo*)
50h: $R^1 = \text{H}$, $R^2 = i\text{-Pr}$: 39% yield, *exo/endo* = 71:29, 68% ee (*exo*)
50i: $R^1 = \text{H}$, $R^2 = p\text{-Tol}$: 63% yield, *exo/endo* = 90:10, 92% ee (*exo*)
50j: $R^1 = \text{H}$, $R^2 = p\text{-EtC}_6\text{H}_4$: 71% yield, *exo/endo* = 93:7, 85% ee (*exo*)
50k: $R^1 = \text{H}$, $R^2 = p\text{-MeOC}_6\text{H}_4$: 74% yield, *exo/endo* = 80:20, 98% ee (*exo*)
50l: $R^1 = \text{H}$, $R^2 = p\text{-BrC}_6\text{H}_4$: 69% yield, *exo/endo* = 94:6, > 98% ee (*exo*)
50m: $R^1 = \text{H}$, $R^2 = \text{OMe}$: 82% yield, *exo/endo* > 99:1, 79% ee (*exo*)

Scheme 15. Lutetium-catalyzed 1,3-dipolar cycloaddition of indoles with diazodiketones and a diazoketoester [29].

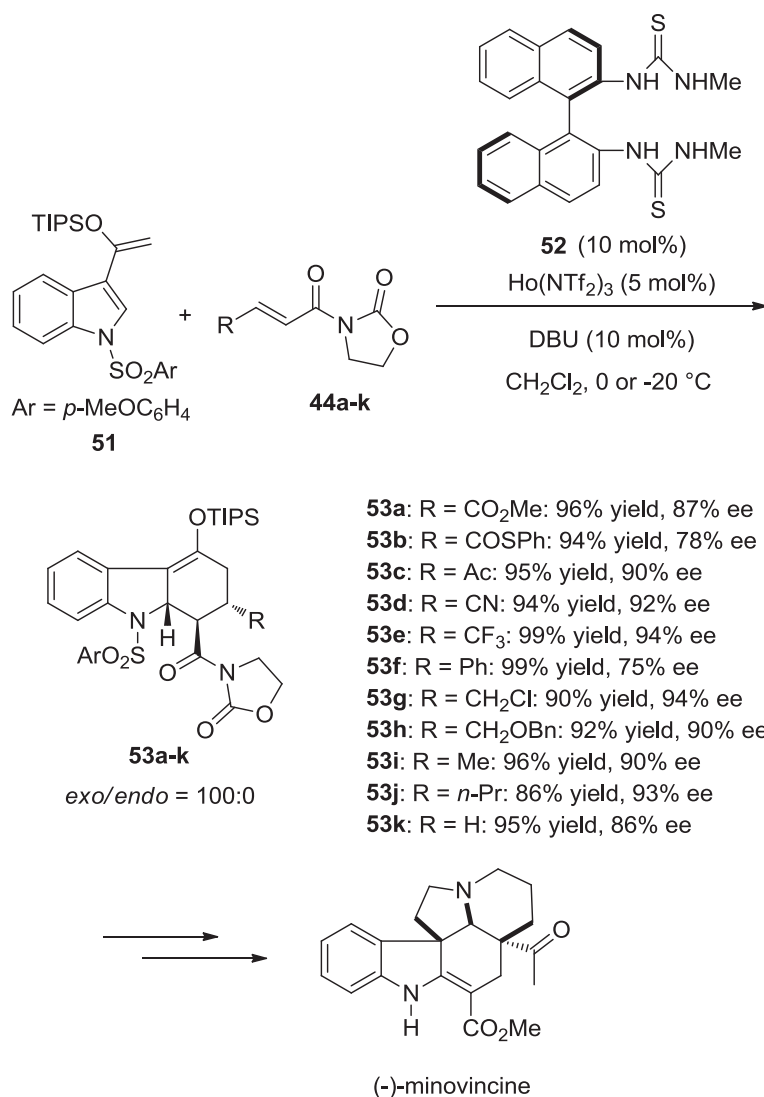
depicted in [Scheme 18](#). A range of cycloadducts **59a–s** was produced in good yields (58–86%) and excellent chemoselectivities combined with moderate diastereoselectivities (1.9:1 to 5.9:1) and enantioselectivities (50–81% ee). Notably, no aldol product was observed. Various substituents at the 5-position of isatins (R^1) including strongly electron-donating methoxy group and strongly electron-withdrawing nitro group as well as *N*-substituted isatins ($R^3 \neq \text{H}$) reacted with α,β -unsaturated methyl ketone **58a** ($R^4 = \text{Ph}$) to give the corresponding products **59j**, **59g**, and **59b–c**, respectively, in good yields (65–82%), moderate diastereoselectivities (1.5:1 to 3.7:1), and moderate enantioselectivities (53–65% ee). Concerning the α,β -unsaturated methyl ketone partner, a range of aromatic substrates were compatible, bearing both electron-withdrawing and electron-donating groups on the benzene rings of R^4 . Furthermore, an alkyl-substituted α,β -unsaturated methyl ketone ($R^4 = i\text{-Pr}$) was also tolerated, giving the corresponding product **59s** in 70% yield, 2:1 dr, and 55% ee. Notably, this work represented the first example of incorporating both an amine catalyst and a metal Lewis acid in direct hetero-Diels–Alder reactions.

In 2014, Trapp and Stockinger reported the asymmetric gadolinium-catalyzed oxa-Diels–Alder cycloaddition of Danishefsky's diene **61** with benzaldehyde **39a** to give the corresponding

cycloadduct **62** after subsequent elimination of trimethylsilanol and methanol with complete conversion and moderate enantioselectivity of 40% ee ([Scheme 19](#)) [36]. This process was promoted by 20 mol% of gadolinium(III)-tris[(1*R*,4*S*)-3-heptafluorobutanoyl-camphor] catalyst **63**. Enantioselectivities are generally moderate for this type of reactions, however, they were slightly better compared to those obtained by using the corresponding europium complex.

3.3. [2+2] cycloadditions

In contrast to the wealth of catalytic systems that are available to control the stereochemistry of thermally promoted cycloadditions, few similarly effective methods exist for the stereocontrol of photochemical cycloadditions. In this context, Yoon et al. have developed asymmetric [2+2] photocycloadditions of α,β -unsaturated ketones using visible light [37]. These processes were based on a dual-catalyst system consisting of a visible light-absorbing transition metal photocatalyst, such as $\text{Ru}(\text{bpy})_3\text{Cl}_2$, and a stereocontrolling Lewis acid co-catalyst, such as $\text{Eu}(\text{OTf})_3$ combined with chiral Schiff base ligand **64**. The crucial activation step in this cycloaddition involved the one-electron reduction of the Lewis acid-activated aryl enone



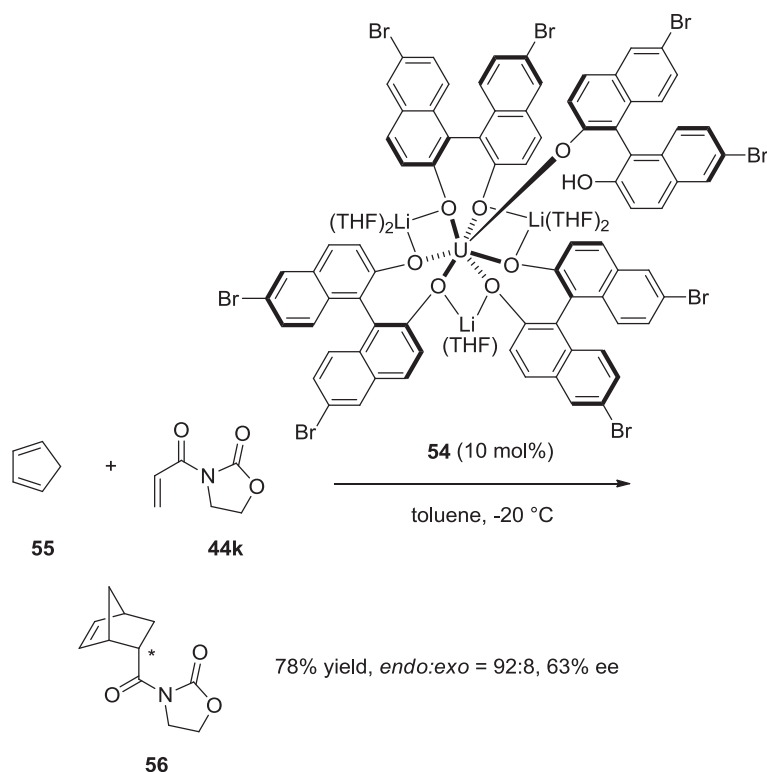
Scheme 16. Holmium-catalyzed Diels–Alder cycloaddition of a 3-[1-(silyloxy)vinyl]indole with *N*-acyloxazolidinones, and synthesis of (–)-minovincine [32].

65 by a ruthenium(I) complex generated by visible light irradiation of Ru(bpy)₃²⁺ in the presence of an amine donor such as *i*-Pr₂NEt. As shown in Scheme 20, the [2+2] cycloaddition of aryl enones **65** with alkyl enones **29a–b** in the presence of this dual catalyst system at room temperature in acetonitrile led to the corresponding chiral cyclobutanes **66** in moderate yields (34–72%), moderate to good diastereoselectivities (42–80% de), and high enantioselectivities (86–93% ee). One important advantage of this dual catalytic system is the functional independence of the photocatalyst and the chiral Lewis acid catalyst, allowing variations in the structure of the ligand to be achieved without any impact on the photochemical properties of the Ru(bpy)₃²⁺ chromophore. In this context, the same reactions were performed in the presence of secondary amine ligand **67** prepared by reduction of ligand **64** by treatment with NaBH₄. Under these related reaction conditions, the cycloaddition of aryl enones **65** with alkyl enones **29a–c** afforded the corresponding cyclobutanes **68** in moderate yields (49–80%), low to moderate diastereoselectivities (20–64% de) albeit with high to excellent enantioselectivities of 84–97% ee (Scheme 20). Notably, using ligand **67** instead of ligand **64** allowed a complementary diastereoselectivity.

4. Enantioselective lanthanide-catalyzed aldol-type reactions

4.1. Direct aldol reactions

The direct catalytic asymmetric aldol reaction is a powerful and atom-economical method to prepare chiral β-hydroxy carbonyl compounds. Many metals, organocatalysts [38], but also more recently lanthanides [39] have been applied to promote these reactions. Actually, the first direct catalytic asymmetric aldol reaction between aldehydes and unmodified ketones was described by Shibasaki et al., in 1999 [40]. The process was promoted by REMB heterobimetallic La/Li catalyst, providing enantioselectivities of up to 93% ee. Later, Pericas, Schelter, and Walsh reinvestigated this reaction, and obtained a comparable enantioselectivity of 95% ee combined to a good yield (74%) in the asymmetric aldol reaction of acetophenone **69** with pivalaldehyde **70** to give the corresponding β-hydroxy ketone **71** [20a]. The process was performed in the presence of air- and water-tolerant rare earth guanidinium BINOLate lanthanum complex **23** as REMB precatalyst that in situ generated, in THF at –20 °C in the presence of catalytic amounts of water as additive and LiI, the corresponding active REMB-type catalyst **72** (Scheme 21).



Scheme 17. Diels–Alder cycloaddition of cyclopentadiene with an *N*-acyloxazolidinone catalyzed by heterobimetallic U/Li/BINOLate complex [34].

In 2016, Dockendorff et al. investigated novel multifunctional heterocyclic chiral ligands in asymmetric metal-catalyzed aldol reactions of 4-nitrobenzaldehyde **39i** with propionaldehyde **73** to provide the corresponding aldol product **74** after subsequent reductive workup by treatment with NaBH_4 in methanol (Scheme 22) [41]. Among a range of metal salts investigated as precatalysts of optimal chiral azole-carboxamide ligand **75**, including $\text{Mg}(\text{OTf})_2$, $\text{Sc}(\text{OTf})_3$, $\text{Cu}(\text{OTf})_2$, ZnBr_2 , $\text{Zn}(\text{OTf})_2$, $\text{Ga}(\text{OTf})_3$, InCl_3 , $\text{In}(\text{OTf})_3$, $\text{Sm}(\text{OTf})_3$, $\text{Eu}(\text{OTf})_3$, $\text{Yb}(\text{OTf})_3$, $\text{Bi}(\text{OTf})_3$, and $\text{Gd}(\text{OTf})_3$, $\text{Zn}(\text{OTf})_2$ provided the best result with 40% yield, *anti:syn* ratio of 85:15, and 85–88% ee. Notably, $\text{Gd}(\text{OTf})_3$ was slightly lower efficient as precatalyst than $\text{Zn}(\text{OTf})_2$ since product **74** was formed in 21% yield, 81:19 *anti:syn* ratio, and 86% ee while the other metal salts all afforded lower enantioselectivities ($\leq 70\%$ ee) as well as lower *anti:syn* ratios ($\leq 69:31$).

4.2. Mukaiyama-aldol reactions

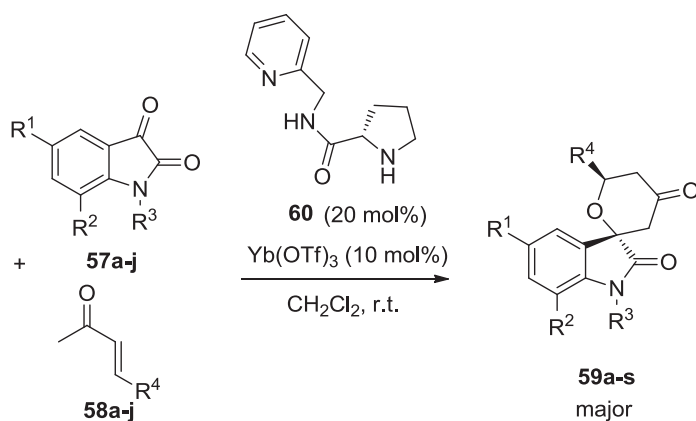
Mukaiyama-aldol reactions constitute useful methods in the total synthesis of complex molecules. Whereas many catalytic asymmetric versions of these reactions have been achieved using various types of chiral Lewis acids [42], the first reaction catalyzed by a chiral lanthanide was reported by Shibasaki et al. only in 1995, providing moderate enantioselectivity of up to 49% ee [43]. The aqueous asymmetric Mukaiyama-aldol reaction catalyzed by chiral water-compatible lanthanide Lewis acids is one of the most attractive reactions for green chemistry. In 2012, Allen et al. developed a novel series of chiral lanthanide-containing complexes that produced Mukaiyama-aldol products with outstanding enantioselectivities of up to 96% ee [44]. As shown in Scheme 23, when a combination of $\text{Nd}(\text{OTf})_3$ with novel chiral ligand **76** was employed as catalyst system in enantioselective Mukaiyama-aldol reactions of aldehydes **77a–g** with trimethylsilyl enol ethers **78a–d**, it led to the corresponding products **79a–m** as major

syn-diastereomers in low to high yields (18–93%), *syn/anti* ratios of 5:1 to $>99:1$, and good to excellent enantioselectivities (78–96% ee). A broad substrate scope was compatible with the precatalyst, including relatively challenging substrates, such as aliphatic aldehydes and silyl enol ethers derived from aliphatic ketones, which afforded the corresponding products **79j–m** and **79f–i** with 90–96% ee and 82–86% ee, respectively.

Later, another excellent result was reported for the same reaction using $\text{Eu}(\text{OTf})_3$ as precatalyst instead of $\text{Nd}(\text{OTf})_3$ [45]. Indeed, the asymmetric aqueous europium-catalyzed Mukaiyama-aldol reaction of benzaldehyde **77a** with trimethylsilyl enol ether **78a**, performed in the presence of the same ligand **76** combined with $\text{Eu}(\text{OTf})_3$, yielded the corresponding *syn*-product **79a** in high yield (92%), high diastereoselectivity (94% de), and excellent enantioselectivity (95% ee), as shown in Scheme 24. NMR measurements and luminescence were used to characterize the coordination environments of the Eu^{3+} -based precatalyst, showing that in the presence of excess hexadentate ligand, Eu^{3+} was coordinatively saturated, and subsequently, the reactivity of the precatalyst was reduced. More specifically, it suggested that two-to-one ligand-to-metal binding for hexadentate ligands occurred in the presence of excess ligand [46].

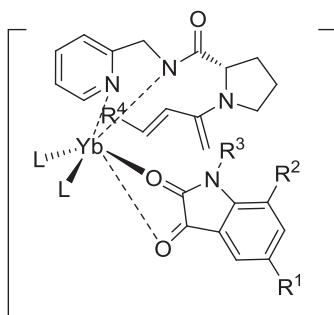
4.3. Nitroaldol reactions

Since the first highly enantioselective nitroaldol or Henry reaction reported by Shibasaki et al. that was based on the use of heterobimetallic La/Li/BINOL complex [47], this group has developed a series of other lanthanide/alkali metal complexes of this type to be applied in these reactions among others. As a recent example, an heterogeneous heterobimetallic Nd/Na complex **80** was prepared by mixing amide-based ligand **81**, $\text{Nd}_5\text{O}(\text{Oi-Pr})_{13}$, and NaHMDS in a 2:1:2 ratio in the presence of nitroethane and THF to afford a white suspension, which was further centrifuged to iso-



- 59a:** $R^1 = R^2 = R^3 = H, R^4 = Ph$: 79% yield, 3:1 dr, 74% ee
59b: $R^1 = R^2 = H, R^3 = Me, R^4 = Ph$: 82% yield, 2.3:1 dr, 65% ee
59c: $R^1 = R^2 = H, R^3 = Bn, R^4 = Ph$: 80% yield, 1.5:1 dr, 61% ee
59d: $R^1 = Cl, R^2 = R^3 = H, R^4 = Ph$: 84% yield, 3.4:1 dr, 59% ee
59e: $R^1 = Br, R^2 = R^3 = H, R^4 = Ph$: 70% yield, 2.9:1 dr, 72% ee
59f: $R^1 = F, R^2 = R^3 = H, R^4 = Ph$: 77% yield, 3.1:1 dr, 50% ee
59g: $R^1 = NO_2, R^2 = R^3 = H, R^4 = Ph$: 65% yield, 2.5:1 dr, 53% ee
59h: $R^1 = R^2 = Me, R^3 = H, R^4 = Ph$: 72% yield, 3.3:1 dr, 67% ee
59i: $R^1 = Me, R^2 = R^3 = H, R^4 = Ph$: 84% yield, 3:1 dr, 60% ee
59j: $R^1 = OMe, R^2 = R^3 = H, R^4 = Ph$: 79% yield, 3.7:1 dr, 54% ee
59k: $R^1 = R^2 = R^3 = H, R^4 = p\text{-Tol}$: 77% yield, 3.6:1 dr, 70% ee
59l: $R^1 = R^2 = R^3 = H, R^4 = p\text{-MeOC}_6\text{H}_4$: 69% yield, 4.3:1 dr, 65% ee
59m: $R^1 = R^2 = R^3 = H, R^4 = p\text{-ClC}_6\text{H}_4$: 75% yield, 1.9:1 dr, 62% ee
59n: $R^1 = R^2 = R^3 = H, R^4 = p\text{-O}_2\text{NC}_6\text{H}_4$: 74% yield, 1.3:1 dr, 73% ee
59o: $R^1 = R^2 = R^3 = H, R^4 = m\text{-O}_2\text{NC}_6\text{H}_4$: 75% yield, 1.4:1 dr, 81% ee
59p: $R^1 = R^2 = R^3 = H, R^4 = 1\text{-Naph}$: 86% yield, 3.6:1 dr, 67% ee
59q: $R^1 = R^2 = R^3 = H, R^4 = 2\text{-Naph}$: 70% yield, 2.7:1 dr, 74% ee
59r: $R^1 = R^2 = R^3 = H, R^4 = 1\text{-thienyl}$: 58% yield, 5.9:1 dr, 60% ee
59s: $R^1 = R^2 = R^3 = H, R^4 = i\text{-Pr}$: 70% yield, 2:1 dr, 55% ee

proposed transition state:

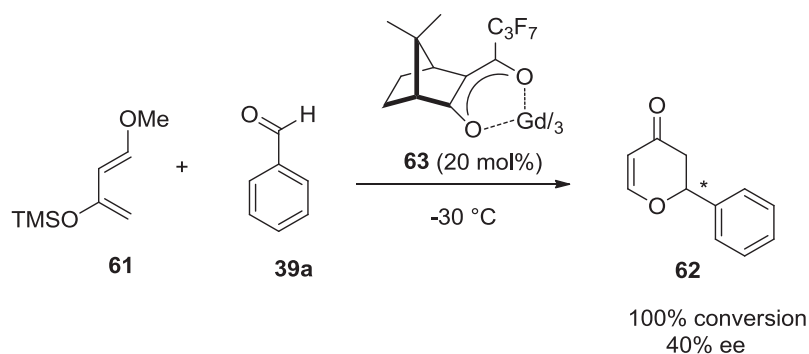


Scheme 18. Ytterbium-catalyzed oxa-Diels-Alder cycloaddition of isatins with α,β -unsaturated methyl ketones [35].

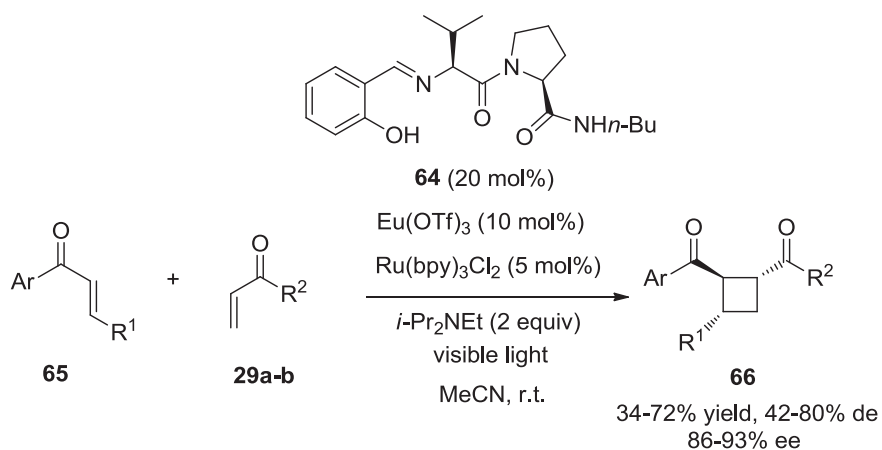
late the precipitate as the active catalyst [48]. The latter promoted the asymmetric nitroaldol reaction of 4-nitro-1-butene **82** with functionalized α,β -unsaturated aldehyde **83** to give the corresponding chiral vicinal nitroalkanol **84** as major *anti*-diastereomer in 71% yield, with *anti/syn* ratio of 10:1, and 94% ee, as shown in Scheme 25. The utility of this methodology was demonstrated in a total synthesis of potent neuraminidase inhibitor zanamivir (Scheme 25).

In 2013, the same group developed self-assembling heterogeneous heterobimetallic Nd/Na chiral catalyst **85** confined in an entangled multiwalled carbon nanotube (MWNT) network [49]. The preparation of this MWNT-confined catalyst from

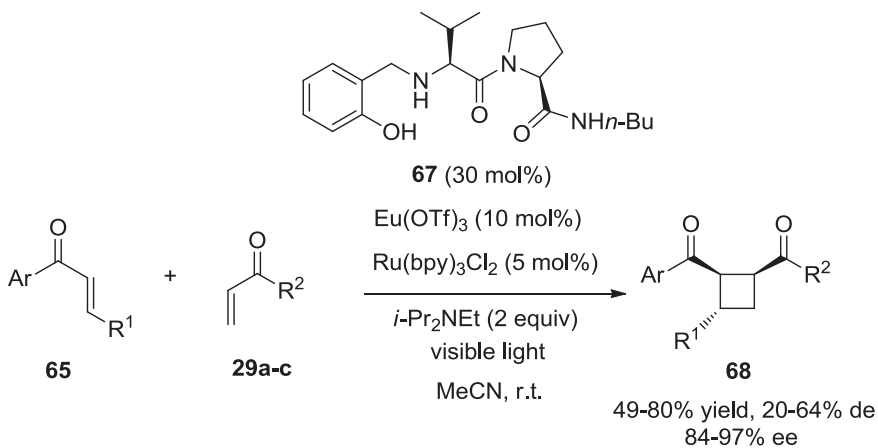
$\text{Nd}_5\text{O}(\text{O}i\text{-Pr})_{13}$, chiral ligand *ent*-**81**, and NaHMDS in a molar ratio of 2:1:2 ratio is illustrated in Scheme 26. Catalyst **85**, generated through self-assembly performed in the presence of MWNT, gave the optimal result in comparison with that was self-assembled before adding MWNT. When 1 mol% of catalyst **85** was used to promote the Henry reaction of aldehydes **77h-1** with nitroalkanes **9a-c**, it led to the corresponding products **86a-g** as major *anti*-diastereomers in moderate to quantitative yields (52–99%), good to excellent *anti/syn* ratios of 83:17 to >98:2, and uniformly high enantioselectivities of 87–99% ee (Scheme 26). This reusable confined catalyst exhibited higher catalytic efficiency than the corresponding unconfined catalyst.



Scheme 19. Gadolinium-catalyzed oxa-Diels-Alder cycloaddition of Danishefsky's diene with benzaldehyde [36].



Ar = Ph, *p*-ClC₆H₄, *p*-BrC₆H₄, *p*-MeOC₆H₄, *m*-MeOC₆H₄, *o*-FC₆H₄, 2-Naph, 1-furyl
R¹ = Me, Et, *i*-Pr, CH₂OBn
R² = Me, Et

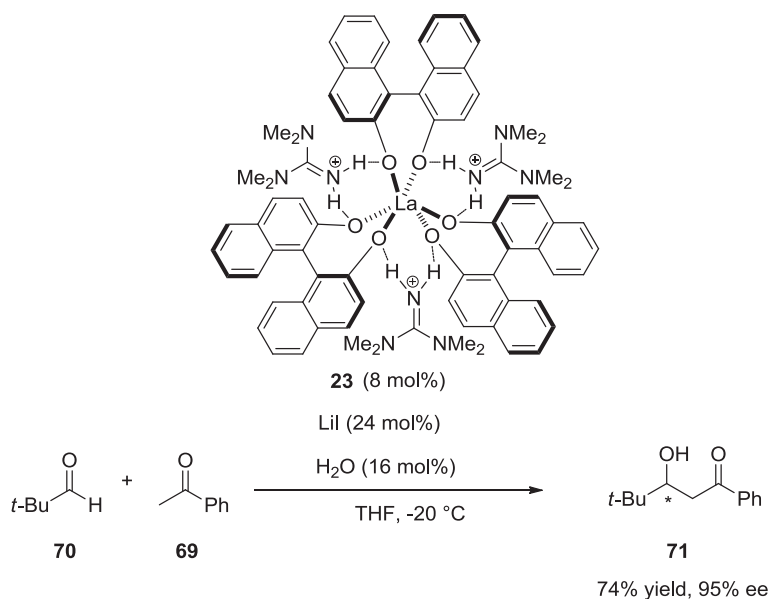


Ar = Ph, *p*-ClC₆H₄, *p*-BrC₆H₄, *p*-MeOC₆H₄, *m*-MeOC₆H₄, *p*-FC₆H₄, 2Naph, 1-furyl
R¹ = Me, *i*-Pr, CH₂OBn
R² = Me, Et, *i*-Bu

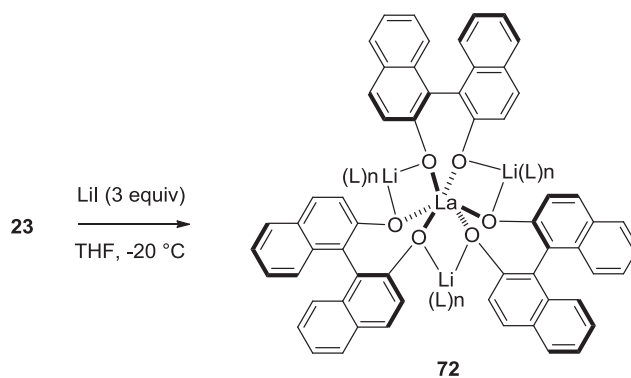
Scheme 20. [2+2] Photocycloadditions of α,β -unsaturated ketones promoted by europium and ruthenium catalysts [37].

As illustrated in [Scheme 27](#), the synthetic utility of catalyst **85** was demonstrated by total syntheses of several drugs, including cholesteryl ester transfer protein inhibitor anacetrapib from product **86a**, β_2 adrenoreceptor agonist ritodrine and β_3 adrenoreceptor agonist **87** both from product **86f**, and prophylactic agent **88** from product **86g** [50].

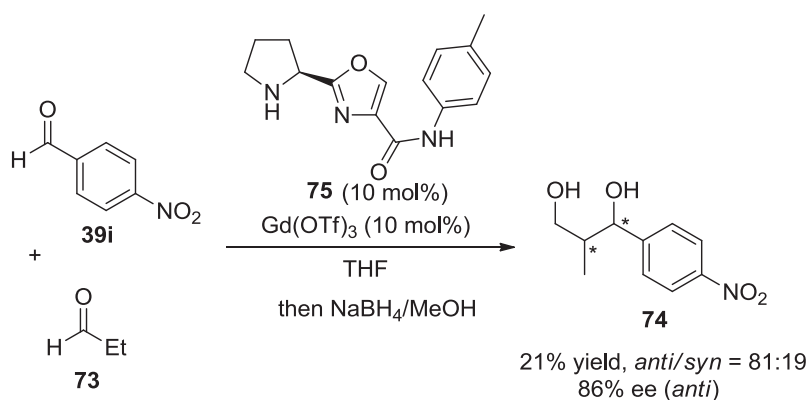
Catalyst **85** could be used in a continuous-flow system, for example in enantioselective Henry reaction of *m*-methoxybenzaldehyde **77m** with nitroethane **9a** [51]. As shown in [Scheme 28](#), the corresponding product **86h** was obtained in 93% yield, *anti/syn* ratio of 93:7, and 88% ee. The flow system obviated the quenching operation, and could be scaled up to produce



in situ preparation of reactive REMB La/Li catalyst **72**:



Scheme 21. Aldol reaction of acetophenone with pivalaldehyde using lanthanum precatalyst **23** [39].

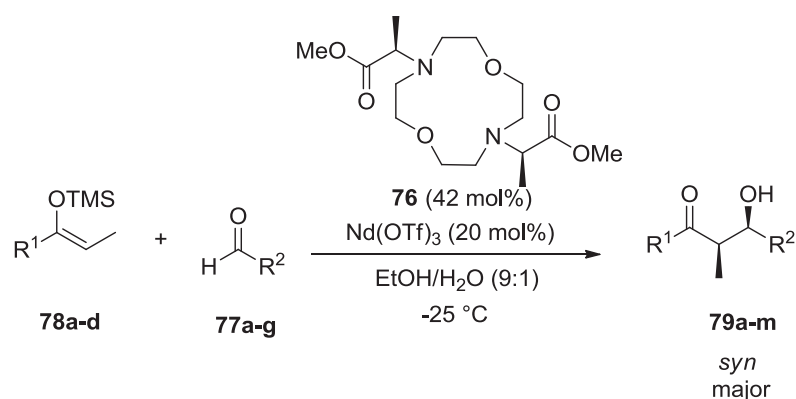


Scheme 22. Gadolinium-catalyzed aldol reaction of 4-nitrobenzaldehyde with propionaldehyde [40].

more than 10 g of products in a minimized cooling volume with more than 200 TON. Chiral nitroaldol product **86h** was further easily transformed into nonsteroidal glucocorticoid receptor agonist AZD5423 (**Scheme 28**).

In spite of the efficiency of the precedent catalysts (**Schemes 25–28**), they present, however, a disadvantage related to the instability and limited availability of Nd₅O(Oi-Pr)₁₃ required for their

preparation. Indeed, this Nd alkoxide is expensive, instable to moisture, and requires handling in a glove box under an inert atmosphere, which hampers its widespread use. To encounter this problem, a novel protocol was described that allowed for catalyst preparation from bench-stable and inexpensive NdCl₃(6H₂O) with comparable activity [52]. As shown in **Scheme 29**, when the asymmetric nitroaldol reaction of aldehydes **77a,i-k,n-r** with



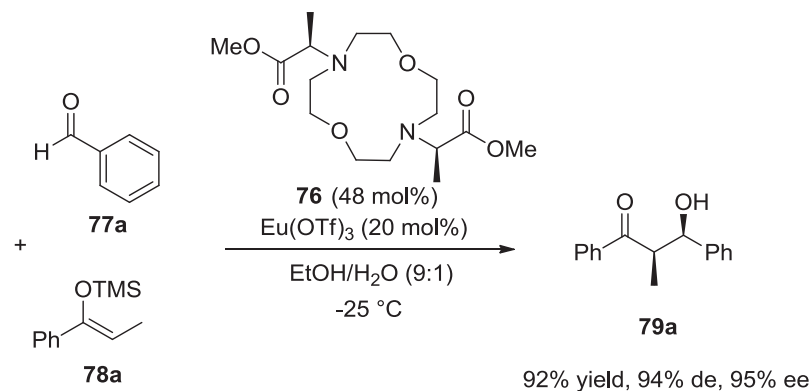
with aromatic aldehydes:

- 79a:** R¹ = R² = Ph: 93% yield, 36:1 *syn/anti*, 92% ee (*syn*)
79b: R¹ = Ph, R² = *p*-ClC₆H₄: 90% yield, 12:1 *syn/anti*, 90% ee (*syn*)
79c: R¹ = Ph, R² = *p*-Tol: 85% yield, 36:1 *syn/anti*, 92% ee (*syn*)
79d: R¹ = Ph, R² = 1-thienyl: 82% yield, > 99:1 *syn/anti*, 88% ee (*syn*)
79e: R¹ = Ph, R² = 1-pyridyl: 55% yield, > 99:1 *syn/anti*, 78% ee (*syn*)
79f: R¹ = Et, R² = Ph: 61% yield, 11:1 *syn/anti*, 84% ee (*syn*)
79g: R¹ = Et, R² = *p*-ClC₆H₄: 39% yield, 9:1 *syn/anti*, 86% ee (*syn*)
79h: R¹ = Et, R² = *p*-Tol: 33% yield, 24:1 *syn/anti*, 84% ee (*syn*)
79i: R¹ = Et, R² = 1-thienyl: 30% yield, > 20:1 *syn/anti*, 82% ee (*syn*)

with aliphatic aldehydes:

- 79j:** R¹ = Ph, R² = (*E*)-Me-CH=CH: 63% yield, 8:1 *syn/anti*, 90% ee (*syn*)
79k: R¹ = Ph, R² = *n*-Hex: 19% yield, 8:1 *syn/anti*, 94% ee (*syn*)
79l: R¹ = *p*-ClC₆H₄, R² = *n*-Hex: 19% yield, 5:1 *syn/anti*, 94% ee (*syn*)
79m: R¹ = *p*-Tol, R² = *n*-Hex: 18% yield, 22:1 *syn/anti*, 96% ee (*syn*)

Scheme 23. Neodymium-catalyzed Mukaiyama-aldol reaction of aldehydes with trimethylsilyl enol ethers [43].



Scheme 24. Europium-catalyzed Mukaiyama-aldol reaction of benzaldehyde with a trimethylsilyl enol ether [44].

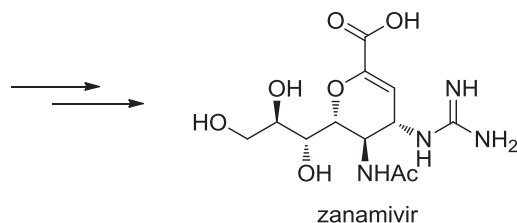
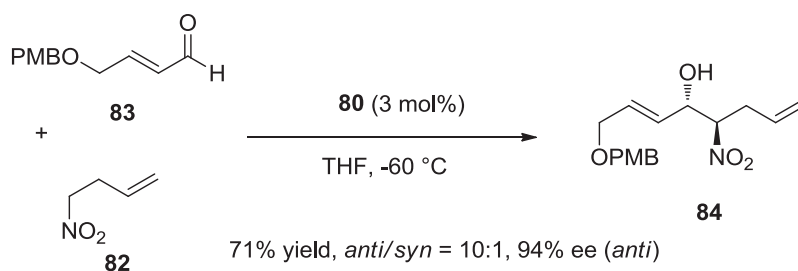
nitroethane **9a** was catalyzed by heterobimetallic Nd/Na/(*ent*)-**81** complex prepared from NdCl₃(6H₂O), it afforded the corresponding chiral nitroaldol products **86d–f,i–n** in very high yields (87–96%), moderate to excellent *anti/syn* diastereoselectivities (*anti/syn* ratios of 3.3:1 to >20:1), and high enantioselectivities of 82–99% ee. These results were compared with those obtained when the catalyst was prepared from the original protocol using Nd₅O(Oi-Pr)₁₃ as precatalyst, and found that they were almost identical.

In 2014, Han and Wang reported asymmetric ytterbium-catalyzed nitroaldol reactions of a variety of aldehydes **77a–c,o,q–y** with nitromethane **5** performed in the presence of novel chiral C₂-symmetric salen ligands bearing morpholine moieties [53]. Ligand **89** was selected as optimal one to afford the corresponding

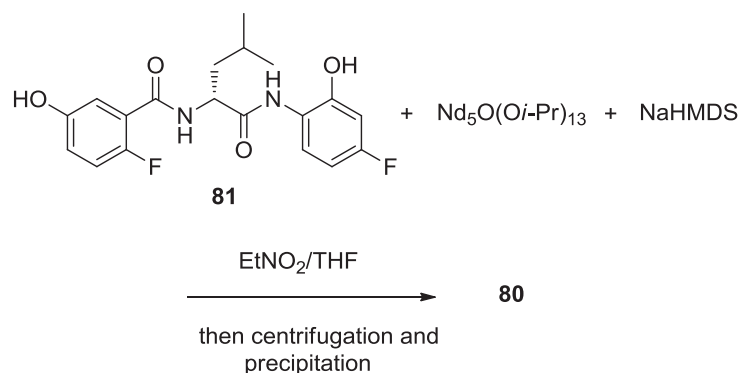
Henry products **86o–aa** in good to high yields (67–98%) and low to good enantioselectivities (10–87% ee), as shown in Scheme 30. The reversal of the enantioselectivity was observed by performing the reaction in the presence of the corresponding cobalt catalyst.

In 2015, Schelter and Walsh reported the enantioselective nitroaldol reaction of cyclohexanecarboxaldehyde **77y** with nitromethane **5** by using heterobimetallic Pr/Li/BINOL catalyst **90** [20c]. As shown in Scheme 31, the corresponding Henry product **86y** was obtained in THF at –40 °C in the presence of a catalytic amount of water in both high yield (95%) and enantioselectivity (90% ee).

In 2016, Zhou et al. developed a novel heterobimetallic catalytic system consisting in 10 mol% of Sm(Oi-Pr)₃, 10 mol% of Cu(OAc)₂,



preparation of heterogeneous catalyst **80**:



Scheme 25. Nitroaldol reaction of 4-nitro-1-butene with a functionalized α,β -unsaturated aldehyde catalyzed by heterobimetallic Nd/Na/**81** complex, and synthesis of zanamivir [47].

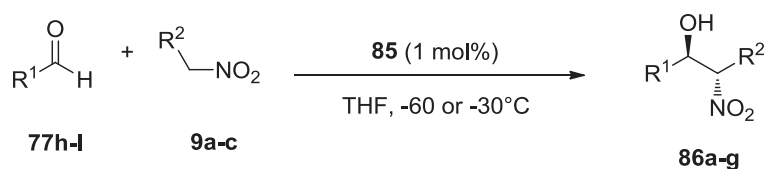
and 10 mol% of chiral aminophenol sulfonamide ligand **91** [54]. When these three partners were mixed in THF at $-30\text{ }^\circ\text{C}$ in the presence of *i*-Pr₂NEt as additive, they generated heterobimetallic complex **92**. When this in situ generated complex was applied to promote the asymmetric Henry reaction of aromatic, heteroaromatic, aliphatic, as well as α,β -unsaturated aldehydes **77a,c,g,s-t, x-ae** with nitroalkanes **9a-b**, it provided the corresponding chiral β -nitroalcohols products (*ent*)-**86i,ab-ao** as major *anti*-diastereomers in moderate to quantitative yields (54–99%), high enantioselectivities (85–98% ee) along with moderate to excellent *anti/syn* ratios of 3:1 to >30:1, as shown in Scheme 32. The lowest yield (54%), diastereoselectivity (*anti/syn* ratio = 3:1), as well as enantioselectivity (85% ee) were observed in the reaction of an aliphatic aldehyde ($R^1 = n\text{-Hex}$) to give product (*ent*)-**86an**.

5. Enantioselective lanthanide-catalyzed epoxidation reactions of alkenes

Chiral epoxides constitute key building blocks for the synthesis of a wide range of important products [55]. In particular, the asymmetric epoxidation of α,β -unsaturated carbonyl compounds is an important and challenging transformation in organic synthesis [56]. Since the first use of chiral lanthanides derived from BINOL as catalysts in these reactions reported by Shibasaki et al. in 1997 [57], other lanthanide-based chiral complexes have been successfully investigated in such reactions. As a recent example,

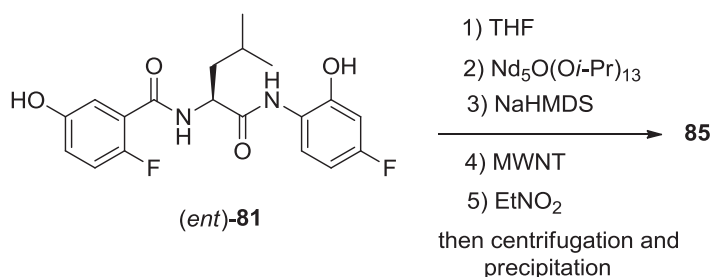
Andrioletti et al. developed enantioselective ytterbium-catalyzed epoxidation of benzylideneacetone **58a** into the corresponding chiral epoxide **93** that was obtained in quantitative yield and high enantioselectivity (90% ee) [58]. The process was performed in the presence of 60 mol% of PPh₃(O) as additive and TBHP as oxidant in THF at $30\text{ }^\circ\text{C}$, and employed a combination of Yb(OTf)₃ with BINOL-derived ligand **94** as catalyst system, as shown in Scheme 33. This novel catalyst displayed the highest catalytic activity and selectivity. Moreover, the selective introduction on the BINOL skeleton of two 3-(dimethylamino)prop-1-yn-1-yl functions constituted a promising approach for the development of a recyclable version of the catalytic system pioneered by Shibasaki et al. Indeed, the corresponding recyclable supported catalyst on silica gel allowed an even higher enantioselectivity of 93% ee to be achieved albeit combined with a moderate yield of 40%.

Later, Tian et al. applied to this reaction the catalyst system earlier reported by Inanaga et al. [59]. This protocol [60] was based on the use of La(Oi-Pr)₃/BINOL/PPh₃(O) complex as catalyst system and TBHP as oxidant in THF at room temperature. When using (*R*)-BINOL as ligand, the process led to chiral epoxide (3*S*,4*R*)-**93** in 90% yield and 97% ee, while the employment of (*S*)-BINOL as ligand provided (3*R*,4*S*)-**93** in 88% yield and 97% ee (Scheme 34). Both the two epoxides were further reduced in the presence of Pd/C and hydrogen in THF at room temperature to give the corresponding odorants 3-hydroxy-4-phenylbutan-2-ones (*S*)- and (*R*)-**95** in 80–81% yields and 90–93% ee.



- 86a:** R¹ = 3,5-I₂C₆H₃, R² = Me: 99% yield, *anti/syn* = 98:2, 99% ee (*anti*)
86b: R¹ = 3,5-I₂C₆H₃, R² = Et: 94% yield, *anti/syn* = 86:14, 93% ee (*anti*)
86c: R¹ = 3,5-I₂C₆H₃, R² = BnOCH₂: 72% yield, *anti/syn* = 83:17, 89% ee (*anti*)
86d: R¹ = BnCH₂, R² = Me: 69% yield, *anti/syn* = 89:11, 87% ee (*anti*)
86e: R¹ = *n*-Oct, R² = Me: 52% yield, *anti/syn* = 84:16, 89% ee (*anti*)
86f: R¹ = *p*-BnOC₆H₄, R² = Me: 97% yield, *anti/syn* > 98:2, 96% ee (*anti*)
86g: R¹ = 3-O₂N-4-BnOC₆H₃, R² = Me: 99% yield, *anti/syn* = 92:8, 88% ee (*anti*)

preparation of catalyst **85**:



Scheme 26. Nitroaldol reaction of aldehydes with nitroalkanes catalyzed by heterobimetallic Nd/Na/(*ent*)-**81** complex confined in a multiwalled carbon nanotube [48].

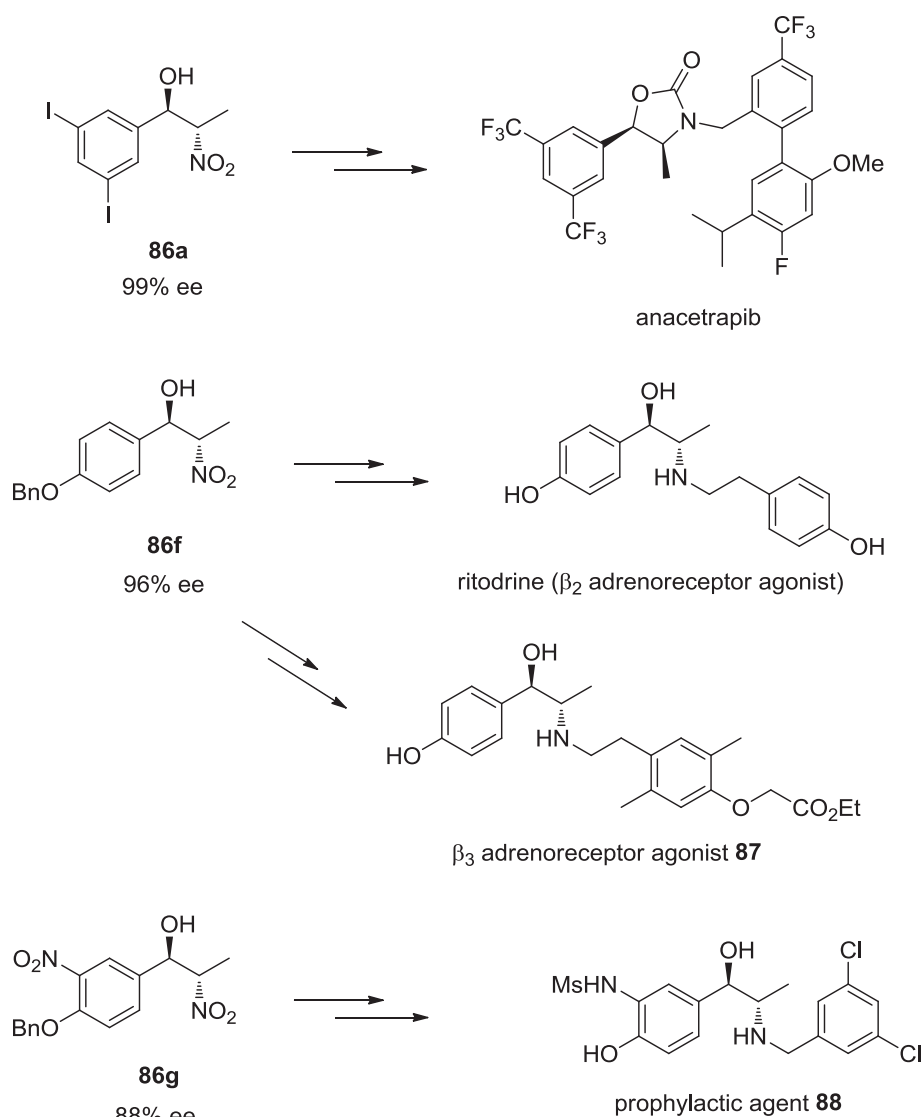
In 2014, Zhao and Yao reported the synthesis of novel heterobimetallic complexes stabilized by chiral phenoxy-functionalized prolinolate, such as Yb/Li complex **96** [61]. As shown in Scheme 35, this catalyst was prepared by treating two equivalents of the corresponding ligand **97** with four equivalents of *n*-BuLi in THF, providing intermediate dilithium salt **98** which was subsequently treated with anhydrous YbCl₃ to give final heterobimetallic Yb/Li/**97** complex **96**. The structure of **96** was established by X-ray diffraction analysis, elemental analysis, and IR spectra. When this preformed chiral complex was applied to promote the asymmetric epoxidation of chalcones **12** in the presence of PPh₃(O) as additive and TBHP as oxidant at 0 °C in acetonitrile as solvent, it afforded the corresponding chiral epoxides **99** in good yields (60–79%) and high enantioselectivities (80–97% ee). The electronic effect of the substituents on the phenyl rings (Ar¹ and Ar²) of the chalcones significantly affected the reaction outcomes. For example, substrates bearing electron-donating groups at the *para*-position of either phenyl ring gave rise to the corresponding products in excellent enantioselectivities (94–99% ee) combined to good yields (65–72%). On the other hand, when electron-donating groups were located at the *ortho*-position of the phenyl rings (Ar¹) adjacent to carbonyl groups, the steric hindrance of the substituents had apparent effect on the enantioselectivity which dropped to 90% ee, comparing with the *para*-substituted ones. When the phenyl rings were substituted with electron-withdrawing groups, the yields increased to 70–79%, while the ee values decreased to 80–92% ee. *para*-methyl-substituted substrate (Ar¹ = *p*-Tol) provided the highest enantioselectivity (99% ee) whereas the *para*-CF₃-substituted substrate (Ar¹ = *p*-CF₃C₆H₄) led to the lowest one (80% ee).

Later, a more simple methodology performed at room temperature using an additive-free catalyst system was developed by the same group [62]. In this case, the combination of only 4 mol% of ytterbium-based amide [(TMS₂N)₃Yb(μ-Cl)Li(THF)₃] with 6 mol

% of chiral ligand **97** in THF at room temperature performed very well in the presence of TBHP as oxidant to epoxidize a range of variously substituted chalcones **12** into the corresponding products **99** in both excellent yields and enantioselectivities of 86–99% and 87–99% ee, respectively (Scheme 36). Even chalcone derivatives **100** bearing an exocyclic double bond also smoothly led to the corresponding chiral trisubstituted α,β-epoxyketones **101** in remarkable enantioselectivities of 94–98% ee combined with good to quantitative yields (82–99%). These products constitute important intermediates in organic synthesis.

6. Enantioselective lanthanide-catalyzed Mannich-type reactions

The asymmetric catalytic Mannich reaction represents a powerful methodology to prepare a number of pharmaceutically and agrochemically relevant products [63]. Although recently various chiral organocatalysts have been successfully applied to promote these reactions, the number of approaches involving chiral metal complexes remains limited. In particular, enantioselective Mannich reactions based on the use of chiral ytterbium catalysts are unexplored. In 2013, Karimi et al. reported a rare example of these reactions, dealing with the Mannich reaction of dibenzyl malonate **102** with *N*-Boc imines **103a–n** that was catalyzed by an ytterbium complex in situ generated from Yb(OTf)₃ and chiral bisoxazoline ligand **104** [64]. Remarkably, the reaction was performed in dichloromethane at room temperature, leading to the corresponding chiral amines **105a–n** in good to excellent yields (59–95%) and enantioselectivities of up to 99% ee, as shown in Scheme 37. In this study, Yb(OTf)₃ was selected as optimal precatalyst among a range of other metal triflates, including Sc(OTf)₃, Cu(OTf)₂, In(OTf)₃, and Zn(OTf)₂ with regard to enantioselectivity (68% ee vs 7–37% ee). This protocol was compatible to a range of aromatic and heteroaromatic *N*-Boc imines **103a–m** that gave the corresponding products



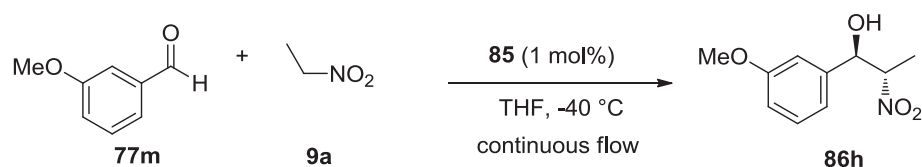
Scheme 27. Application in syntheses of drugs [49].

105a–m with the highest yields (83–95%) and enantioselectivities (89–99% ee). In the case of aromatic substrates **103a–k**, the position and electronic nature of the substituents on the aromatic ring had a very limited influence on the enantioselectivity. On the other hand, aliphatic *N*-Boc imine **103n** ($R = \text{Cy}$) led to the corresponding product **105n** in both lower yield (59%) and enantioselectivity (69% ee). It must be noted that this novel methodology represented the first example of highly enantioselective metal-catalyzed Mannich reaction of malonate esters performed at room temperature.

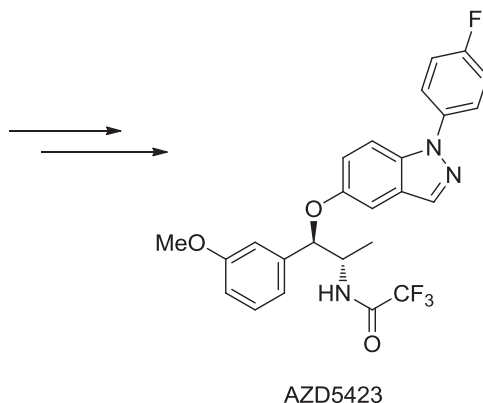
In 2015, a heterogeneous erbium complex confined in an entangled multiwalled carbon nanotube (MWNT) **106** was applied by Shibasaki et al. to the asymmetric Mannich-type reaction of α -cyanoketone **107** with various *N*-Boc arylimines **103a,e–g,i–j,l** to give the corresponding chiral Mannich products **108a–g**, as shown in Scheme 38 [65]. Remarkably, these products were uniformly achieved in excellent yields (90–99%), *syn/anti* ratios of 94:6 to 97:3, and enantioselectivities (93–98% ee). Recyclable and easily handled solid-phase catalyst **106** was generated by self-assembly of dimeric chiral ligand **109** having a undecyl linker with $\text{Er}(\text{O}i\text{-Pr})_3$ in an MWNT network, as illustrated in Scheme 38. Moreover, this heterogeneous MWNT-confined catalyst allowed repetitive use and gram-scale reaction in a batch system as well as in a continuous-flow platform.

7. Enantioselective lanthanide-catalyzed 1,2-nucleophilic additions to carbonyl compounds and imines

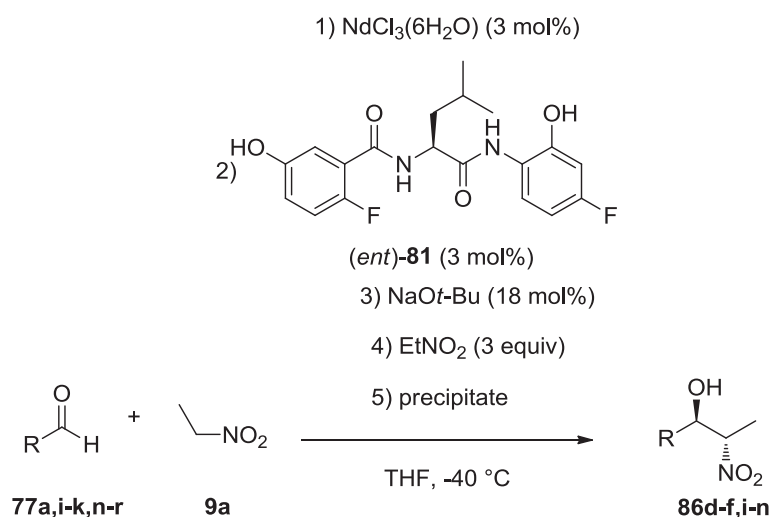
Reactions involving in situ generated highly reactive oxocarbenium ions are challenging due to their usefulness in the synthesis of complex natural products and biologically active compounds. In 2012, Rueping et al. developed the first asymmetric addition of aldehydes **110** to oxocarbenium ions in situ generated from chromene acetals **111**, allowing the synthesis of the corresponding chiral chromenes **112** bearing two stereogenic centers after subsequent reduction with NaBH_4 [66]. As shown in Scheme 39, this process was performed through dual catalysis by using a combination of $\text{Yb}(\text{OTf})_3$ as achiral Lewis acid and chiral imidazolidinone organocatalyst **113** that simultaneously activated the electrophile and the nucleophile. Indeed, the reaction evolved through the formation of chiral enamine **114** by reaction between aldehyde **110** and amine organocatalyst **113** which subsequently added to oxocarbenium ion **115** in situ generated from chromene acetal **111** in the presence of $\text{Yb}(\text{OTf})_3$, as shown in Scheme 39. A range of differently substituted chromene acetals and aldehydes were tolerated, leading to chiral chromenes **112** in good to high yields (69–89%) and enantioselectivities (72–97% ee) albeit combined with moderate diastereoselectivities (28–48% de).



93% yield, *anti/syn* = 93:7, 88% ee (*anti*)



Scheme 28. Continuous-flow nitroaldol reaction of *m*-methoxybenzaldehyde with nitroethane catalyzed by heterobimetallic Nd/Na/(*ent*)-**81** complex confined in a multiwalled carbon nanotube, and synthesis of AZD5423 [50].



86d: R = BnCH₂: 94% yield, *anti/syn* = 4.4:1, 82% ee (*anti*)

86e: R = *n*-Oct: 90% yield, *anti/syn* = 3.3:1, 85% ee (*anti*)

86f: R = *p*-BnOC₆H₄: 87% yield, *anti/syn* > 20:1, 99% ee (*anti*)

86i: R = Ph: 96% yield, *anti/syn* > 20:1, 93% ee (*anti*)

86j: R = 2,4-Me₂C₆H₃: 95% yield, *anti/syn* > 20:1, 99% ee (*anti*)

86k: R = *p*-NCC₆H₄: 91% yield, *anti/syn* = 19:1, 97% ee (*anti*)

86l: R = *p*-MeO₂CC₆H₄: 92% yield, *anti/syn* > 20:1, 96% ee (*anti*)

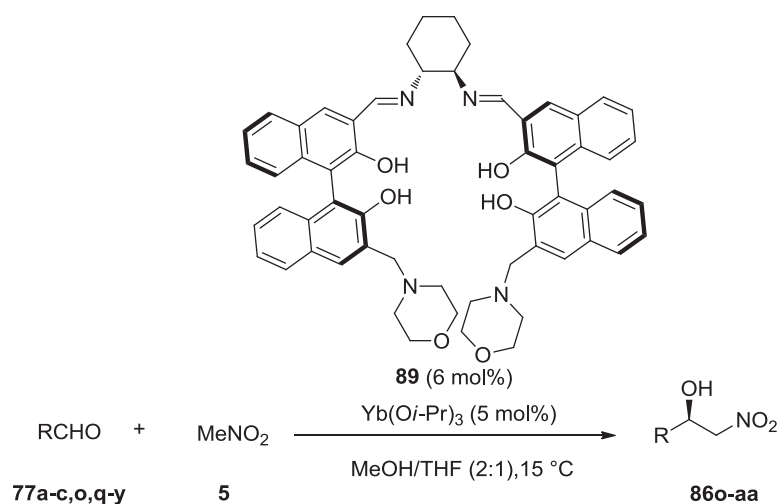
86m: R = *p*-O₂NC₆H₄: 92% yield, *anti/syn* = 6.5:1, 88% ee (*anti*)

86n: R = Cy: 90% yield, *anti/syn* = 6.8:1, 94% ee (*anti*)

Scheme 29. Nitroaldol reaction of aldehydes with nitroethane catalyzed by heterobimetallic Nd/Na/(*ent*)-**81** complex prepared from $\text{NdCl}_3(6\text{H}_2\text{O})$ [51].

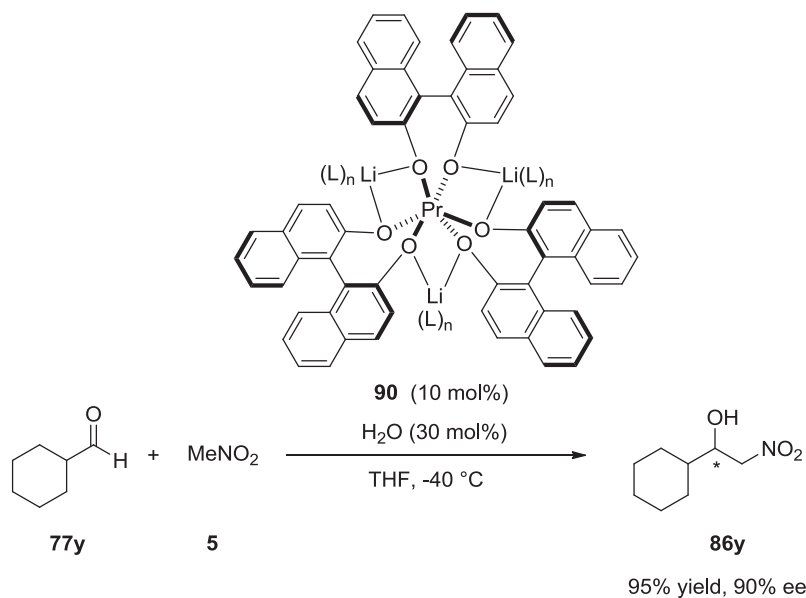
In 2016, Liu and Feng reported the enantioselective scandium-catalyzed addition of 3,3-dimethylindolin-2-one **116** to 2*H*-azirines **117** performed in the presence of a combination of Sc(OTf)₃ and *N,N*-dioxide ligand **118** in a mixed solvent of toluene and Et₂O at 35 °C [67]. As shown in Scheme 40, the process

afforded the corresponding chiral aziridines **119** bearing two contiguous stereogenic centers in moderate yields (30–67%) and low to excellent enantioselectivities (25–99% ee). Interestingly, the reaction evolved through kinetic resolution and enantioenriched (*R*)-2*H*-azirines **117** were recovered in moderate to good



- 86o:** R = Ph: 93% yield, 87% ee
86p: R = *p*-ClC₆H₄: 77% yield, 37% ee
86q: R = *p*-O₂NC₆H₄: 96% yield, 16% ee
86r: R = *p*-NCC₆H₄: 98% yield, 12% ee
86s: R = *p*-F₃CNC₆H₄: 85% yield, 10% ee
86t: R = *p*-FC₆H₄: 84% yield, 58% ee
86u: R = *o*-FC₆H₄: 91% yield, 51% ee
86v: R = *m*-FC₆H₄: 92% yield, 65% ee
86w: R = *p*-Tol: 89% yield, 66% ee
86x: R = *p*-MeOC₆H₄: 81% yield, 62% ee
86y: R = Cy: 67% yield, 52% ee
86z: R = 2-furyl: 87% yield, 33% ee
86aa: R = (*E*)-PhCH=CH: 84% yield, 38% ee

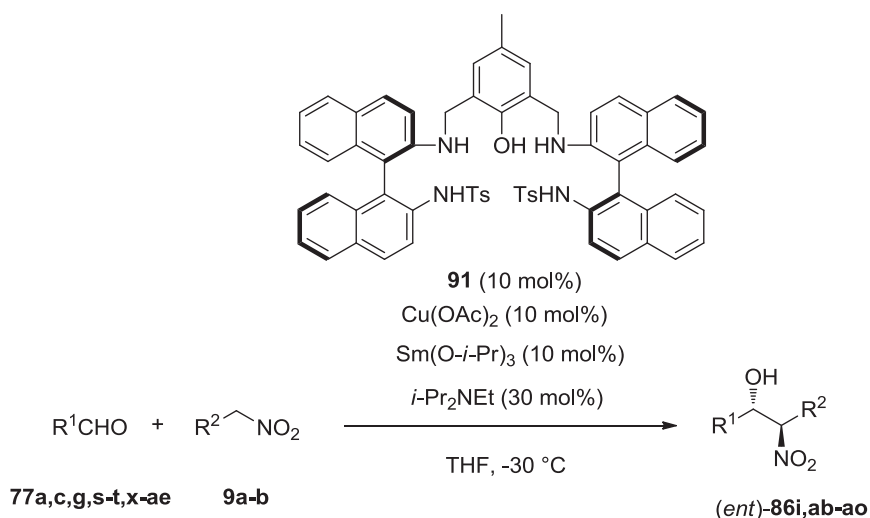
Scheme 30. Ytterbium-catalyzed nitroaldol reaction of aldehydes with nitromethane [52].



Scheme 31. Nitroaldol reaction of cyclohexanecarboxaldehyde with nitromethane promoted by heterobimetallic Pr/Li/BINOL catalyst [20c].

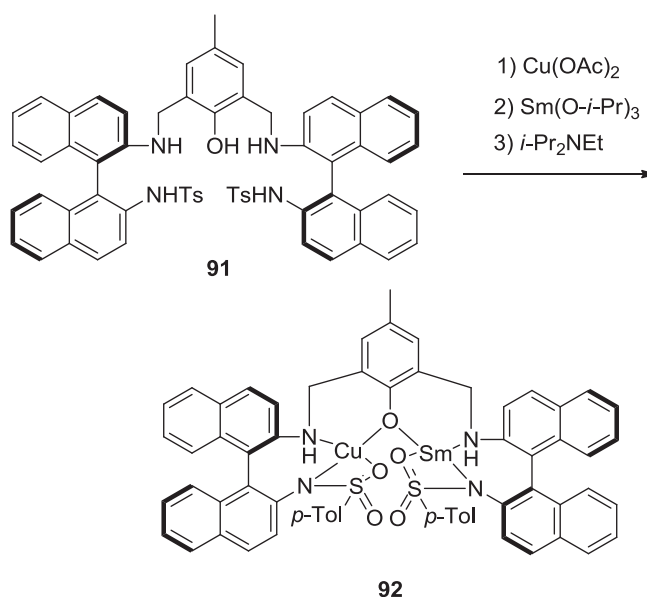
conversion (19–50%) and good to excellent enantioselectivities (64–>99% ee). 2*H*-Azirines containing either electron-withdrawing or electron-donating substituents on the 4-position of the phenyl ring (R¹) were smoothly converted into the

corresponding products **119** in good yields (46–53%) and excellent enantioselectivities (81–99% ee). Substrate **117** having a naphthyl substituent also gave good results since the corresponding product **119** was obtained in 56% yield, and 92% ee. Although alkyl groups

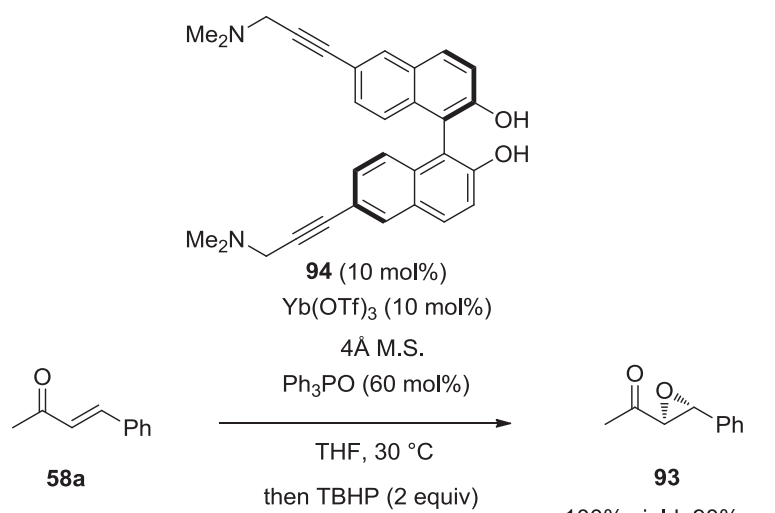


- (ent)-86i*: $R^1 = \text{Ph}$, $R^2 = \text{Me}$: 90% yield, *anti/syn* = 14:1, 93% ee (*anti*)
(ent)-86ab: $R^1 = o\text{-O}_2\text{NC}_6\text{H}_4$, $R^2 = \text{Me}$: 99% yield, *anti/syn* > 30:1, 96% ee (*anti*)
(ent)-86ac: $R^1 = p\text{-F}_3\text{CC}_6\text{H}_4$, $R^2 = \text{Me}$: 99% yield, *anti/syn* = 11:1, 92% ee (*anti*)
(ent)-86ad: $R^1 = p\text{-FC}_6\text{H}_4$, $R^2 = \text{Me}$: 99% yield, *anti/syn* = 14:1, 92% ee (*anti*)
(ent)-86ae: $R^1 = o\text{-Tol}$, $R^2 = \text{Me}$: 68% yield, *anti/syn* = 16:1, 89% ee (*anti*)
(ent)-86af: $R^1 = p\text{-Tol}$, $R^2 = \text{Me}$: 77% yield, *anti/syn* = 12:1, 94% ee (*anti*)
(ent)-86ag: $R^1 = 2\text{-furyl}$, $R^2 = \text{Me}$: 96% yield, *anti/syn* = 20:1, 94% ee (*anti*)
(ent)-86ah: $R^1 = 5\text{-Br-2-furyl}$, $R^2 = \text{Me}$: 99% yield, *anti/syn* = 24:1, 94% ee (*anti*)
(ent)-86ai: $R^1 = (E)\text{-PhCH=CH}$, $R^2 = \text{Me}$: 97% yield, *anti/syn* > 30:1, 98% ee (*anti*)
(ent)-86aj: $R^1 = p\text{-MeOC}_6\text{H}_4$, $R^2 = \text{Me}$: 68% yield, *anti/syn* = 11:1, 92% ee (*anti*)
(ent)-86ak: $R^1 = 1\text{-Naph}$, $R^2 = \text{Me}$: 93% yield, *anti/syn* = 24:1, 88% ee (*anti*)
(ent)-86al: $R^1 = 2\text{-Naph}$, $R^2 = \text{Me}$: 99% yield, *anti/syn* = 14:1, 92% ee (*anti*)
(ent)-86am: $R^1 = 2\text{-thienyl}$, $R^2 = \text{Me}$: 78% yield, *anti/syn* = 16:1, 95% ee (*anti*)
(ent)-86an: $R^1 = n\text{-Hex}$, $R^2 = \text{Me}$: 54% yield, *anti/syn* = 3:1, 85% ee (*anti*)
(ent)-86ao: $R^1 = \text{Ph}$, $R^2 = \text{Et}$: 56% yield, *anti/syn* = 20:1, 86% ee (*anti*)

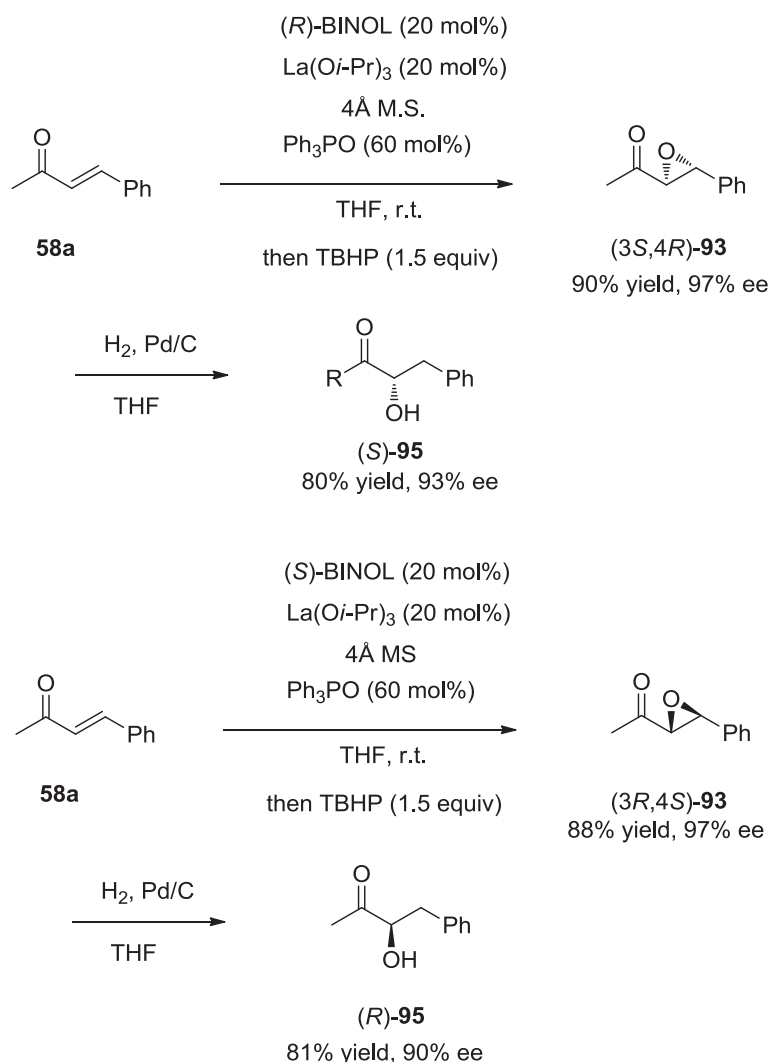
formation of active catalyst **92**:



Scheme 32. Nitroaldol reaction of aldehydes with nitroalkanes promoted by heterobimetallic Sm/Cu/**91** complex [53].



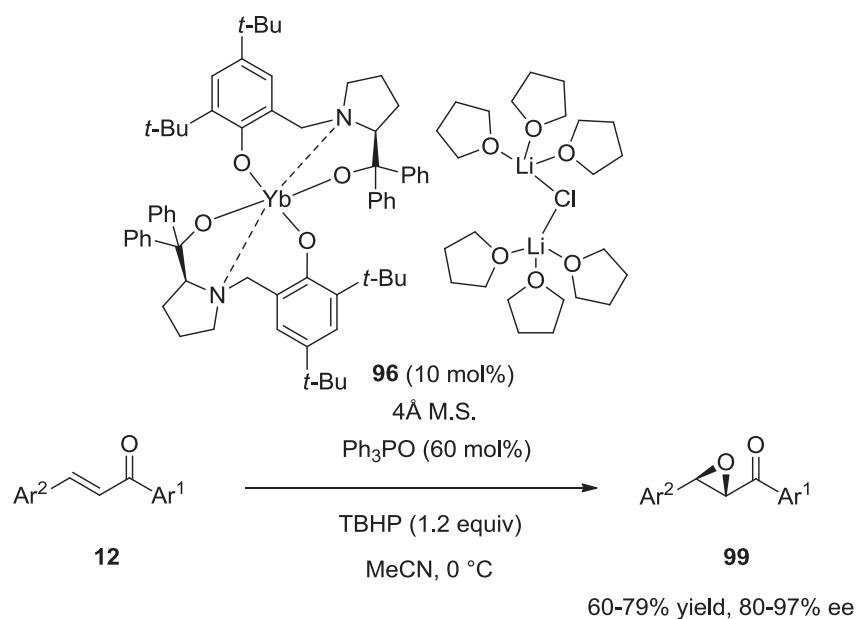
Scheme 33. Ytterbium-catalyzed epoxidation of benzylideneacetone [57].



Scheme 34. Lanthanum-catalyzed epoxidations of benzylideneacetone, and synthesis of odorants [58].

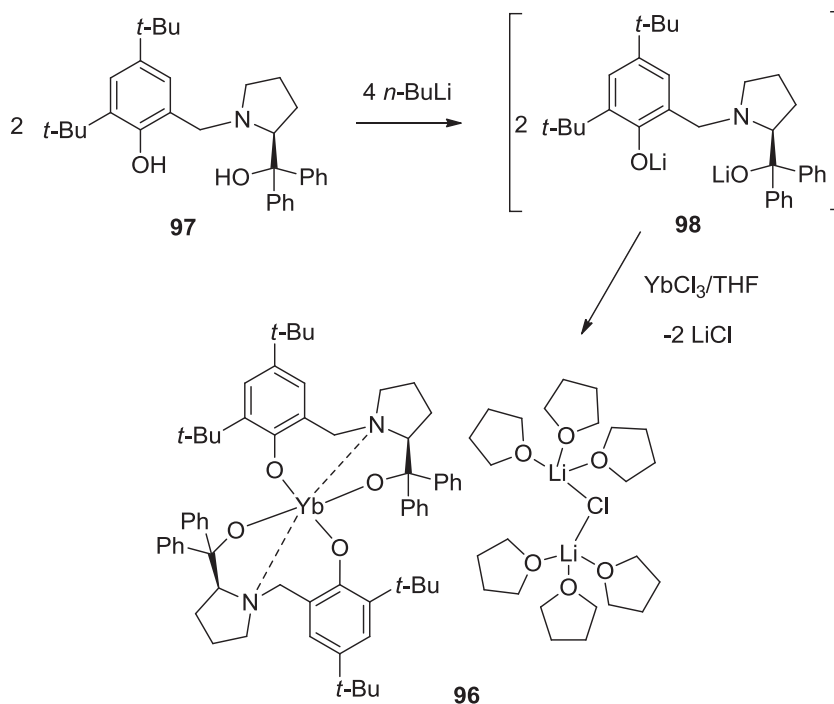
on the 3-position (R^1) of the 2*H*-azirine were compatible, the substrate having a methyl group ($R^1 = \text{Me}$, $R^2 = \text{Ph}$) provided a low enantioselectivity (30% ee). In addition to unsubstituted phenyl

group, the R^2 substituent of the 2*H*-azirine could be substituted at the 4-position by electron-donating as well as electron-withdrawing groups since the corresponding products **119** were



Ar¹ = Ph, *p*-ClC₆H₄, *p*-MeOC₆H₄, *p*-Tol, *p*-(*n*-Pent)C₆H₄, *o*-Tol, 1-furyl
 Ar² = Ph, *p*-MeOC₆H₄, *p*-Tol, *p*-(*i*-Pr)C₆H₄, *p*-ClC₆H₄, *m*-ClC₆H₄,
p-BrC₆H₄, *p*-FC₆H₄, *o*-FC₆H₄, *p*-F₃CC₆H₄, *o*-Tol, *o*-MeOC₆H₄, 2-Naph

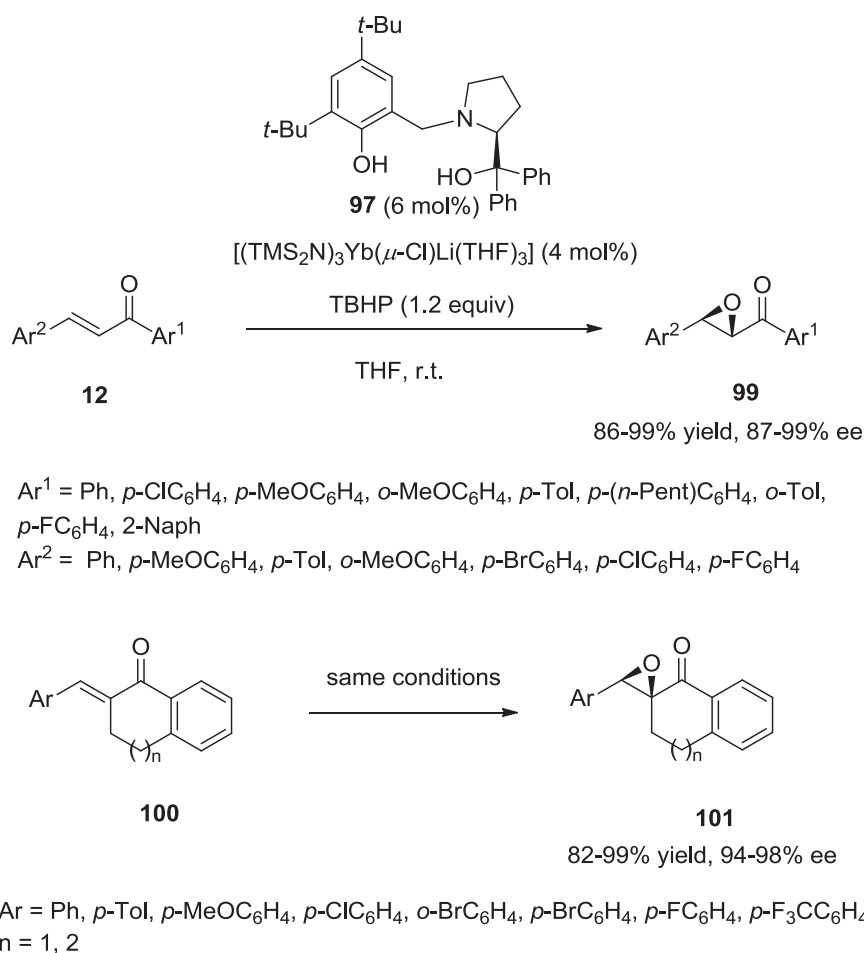
preparation of catalyst **96**:



Scheme 35. Epoxidation of chalcones catalyzed by preformed heterobimetallic Yb/Li/**97** complex **96** [60].

achieved in uniformly excellent enantioselectivities of 92–95% ee. On the other hand, when R² was an alkyl group, the corresponding product **119** was obtained with the lowest enantioselectivity (25% ee) while the ee value of the recovered (*R*)-2*H*-azirine **117** was of 78%. In almost all cases of substrates, the recovered (*R*)-2*H*-azirines **117** were obtained in excellent enantioselectivities of 92–99% ee with the exception of 2*H*-azirines bearing a methyl

group (R¹ = Me), or a *o*-tolyl group (R¹ = *o*-Tol), which were recovered in lower ee values (57–64%). This study represented the first kinetic resolution of 2*H*-azirines through an asymmetric imine amidation under mild reaction conditions. The formed molecules constitute key intermediates in organic synthesis as well as privileged structural units in a number of natural products and biologically relevant compounds.



Scheme 36. Ytterbium-catalyzed epoxidations of chalcones without additive [61].

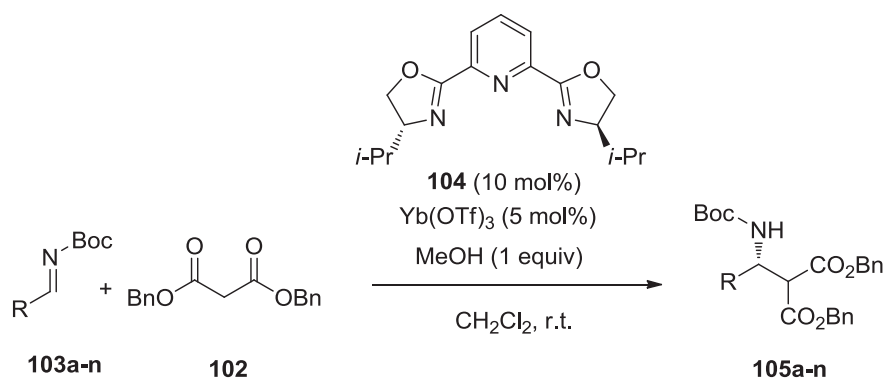
In 2013, Schelter and Walsh reported the first examples of substitution of the peripheral metal cations in Shibasaki-type REMB catalysts with the introduction of Zn^{2+} , resulting in the synthesis and characterization of rare earth-zinc ethyl heterobimetallic complexes, $(\text{EtZn})_3(\text{THF})_2(\text{BINOLate})_3\text{RE}^{\text{III}}(\text{THF})$ [68]. For example, heterobimetallic Eu/Zn complex **120** derived from (*S*)-BINOL, the structure of which was characterized by single-crystal X-ray diffraction, was easily prepared by mixing in THF at room temperature one equivalent of $\text{Eu}[\text{N}(\text{TMS})_2]_3$, three equivalents of (*S*)-BINOL, and three equivalents of ZnEt_2 (Scheme 41). This catalyst could promote the asymmetric addition of ZnEt_2 to benzaldehyde **39a** in toluene at room temperature in the presence of $\text{PPh}_3(\text{O})$ as additive to give the corresponding chiral alcohol **121** in quantitative yield and promising enantioselectivity of 70% ee (Scheme 41).

8. Enantioselective lanthanide-catalyzed Friedel-Crafts reactions

In spite of the importance of the Friedel-Crafts reaction in organic chemistry [69]; enantioselective catalytic versions are still unexplored even if a variety of chiral Lewis acids or organocatalysts have been recently developed for this type of reactions involving different substrates including nitroalkenes. In particular, the useful asymmetric Friedel-Crafts reaction between these substrates and indoles have recently known great advances by using chiral Lewis and Brønsted acid catalysts [70]. However, the

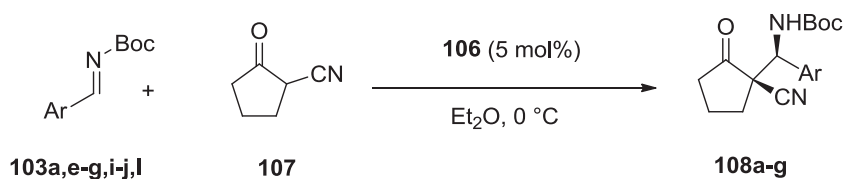
asymmetric Friedel-Crafts alkylations of pyrroles are less explored due to the relative instability of these compounds towards acidic environments. A rare example of this type of reactions was developed in 2012 by Zhang, occurring between unprotected pyrroles **122** and nitroalkenes **123** [71]. As shown in Scheme 42, it afforded the corresponding chiral pyrrole derivatives **124** in moderate to high yields (55–95%) and enantioselectivities (50–93% ee). While multimetallic complexes have been rarely reported for this type of reactions [72], this one was carried out by using a novel chiral heterotrimeric $\text{Pd}/\text{Sm}/\text{Pd}$ catalyst **125** in situ generated from 2.5 mol% of $\text{Sm}(\text{OTf})_3$, 5 mol% of $\text{Pd}(\text{OAc})_2$, and 5 mol% of chiral reduced Schiff base **126** in THF at room temperature. The structure of this complex was characterized by X-ray crystallography. Several aryl-substituted nitroalkenes **123**, containing both electron-donating and electron-withdrawing groups, provided the corresponding products **124** in high yields (92–94%) and good enantioselectivities (71–91% ee). Heteroaryl-substituted nitroalkenes were also tolerated with the thiophene-derived substrate giving the highest ee value (93% ee). In contrast, an alkyl-substituted ($\text{R}^2 = n\text{-Bu}$) provided much lower yield and enantioselectivity (55% yield, 59% ee). In addition to unsubstituted pyrrole ($\text{R}^1 = \text{H}$), the pyrrole bearing an ethyl substituent ($\text{R}^1 = \text{Et}$) was compatible although in some cases only inferior enantioselectivities (50–66% ee) were obtained.

To continue his efforts in asymmetric multimetallic catalyzed Friedel-Crafts reactions, this author later reported the same type of reaction occurring between indoles **127** and nitroalkenes **123** in the presence of another novel heterotrimeric $\text{Cu}/\text{Eu}/\text{Cu}$ chiral



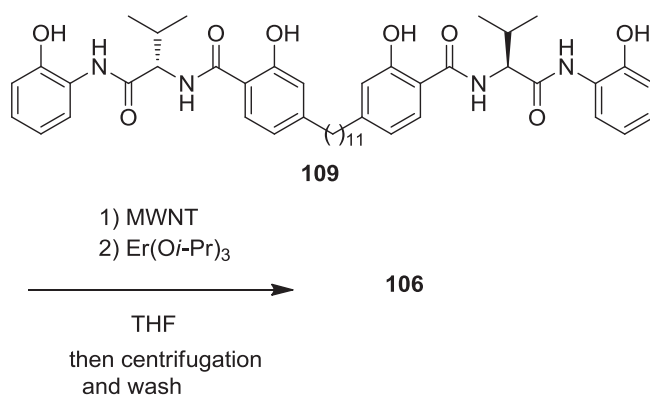
- 105a:** R = Ph: 91% yield, 95% ee
105b: R = *o*-BrC₆H₄: 88% yield, 93% ee
105c: R = *m*-BrC₆H₄: 95% yield, 97% ee
105d: R = *p*-BrC₆H₄: 94% yield, 98% ee
105e: R = *o*-ClC₆H₄: 91% yield, 93% ee
105f: R = *p*-ClC₆H₄: 95% yield, 96% ee
105g: R = *o*-Tol: 88% yield, 92% ee
105h: R = *m*-Tol: 88% yield, 95% ee
105i: R = *p*-Tol: 92% yield, 99% ee
105j: R = *p*-MeOC₆H₄: 83% yield, 98% ee
105k: R = *p-i*-PrC₆H₄: 92% yield, 93% ee
105l: R = 2-Naph: 85% yield, 89% ee
105m: R = 2-furyl: 91% yield, 96% ee
105n: R = Cy: 59% yield, 69% ee

Scheme 37. Ytterbium-catalyzed Mannich-type reaction of dibenzyl malonate with *N*-Boc imines [63].

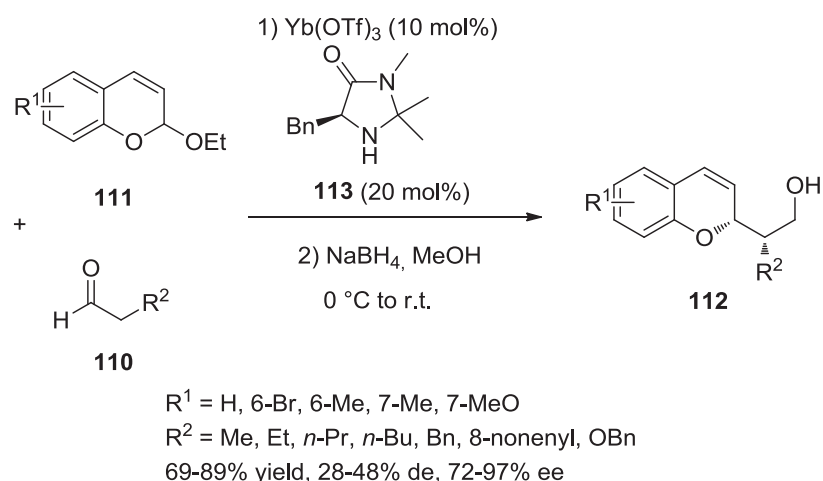


- 108a:** Ar = Ph: 98% yield, *syn/anti* = 94:6, 96% ee
108b: Ar = 2-Naph: 99% yield, *syn/anti* = 97:3, 95% ee
108c: Ar = *o*-Tol: 99% yield, *syn/anti* = 97:3, 98% ee
108d: Ar = *p*-Tol: 99% yield, *syn/anti* = 94:6, 97% ee
108e: Ar = *o*-ClC₆H₄: 99% yield, *syn/anti* = 97:3, 97% ee
108f: Ar = *p*-ClC₆H₄: 90% yield, *syn/anti* = 97:3, 93% ee
108g: Ar = *p*-MeOC₆H₄: 99% yield, *syn/anti* = 94:6, 93% ee

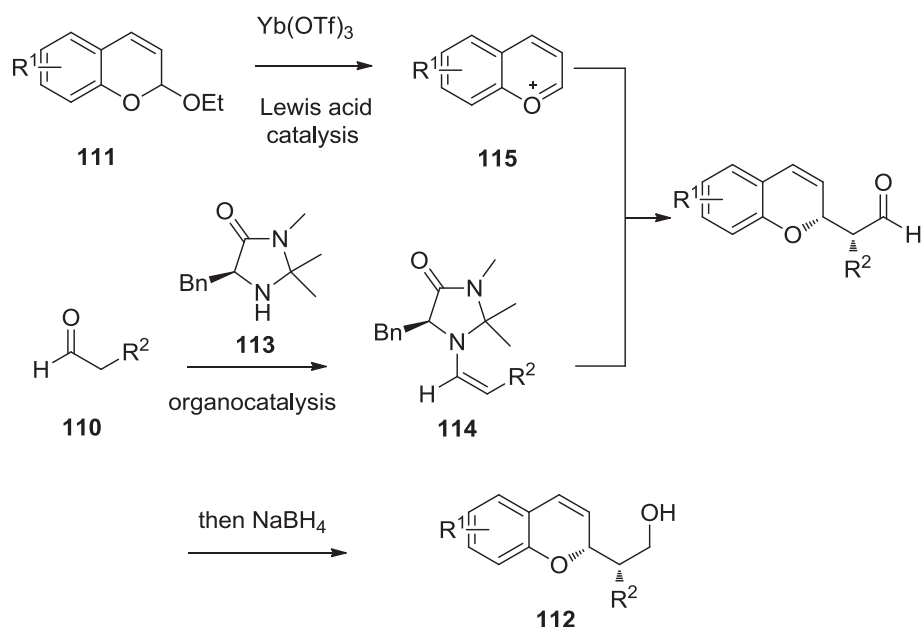
preparation of catalyst **106**:



Scheme 38. Mannich-type reaction of a α -cyanoketone with *N*-Boc arylimines catalyzed by heterogeneous Er/**109** complex confined in a multiwalled carbon nanotube [64].



proposed mechanism through dual catalysis:



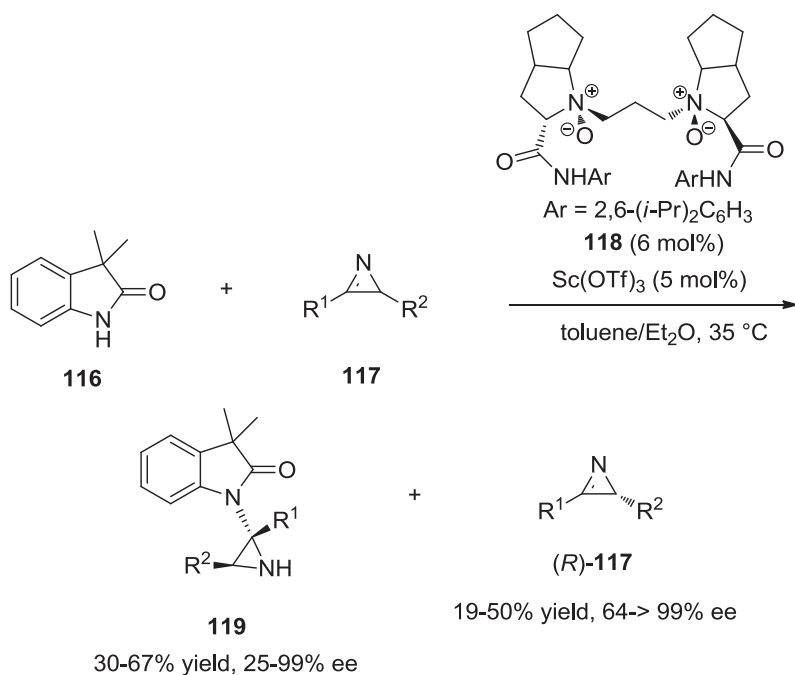
Scheme 39. Addition of aldehydes to oxocarbenium ions derived from chromene acetals through dual ytterbium/organocatalysis [65].

complex **128** [73]. As shown in [Scheme 43](#), the active catalyst **128** was in situ generated in toluene at room temperature from 5 mol% of $\text{Cu}(\text{OAc})_2$, 2.5 mol% of $\text{Eu}(\text{OTf})_3$, and 5 mol% of the same chiral ligand **126**. Isolated complex **128** was structurally characterized by X-ray crystallography. Under these mild reaction conditions, the process produced various chiral indole derivatives **129** in moderate to high yields (55–88%) and enantioselectivities (49–80% ee). Unprotected and *N*-methylindoles were tolerated as well as a range of aromatic nitroalkenes bearing either electron-donating or electron-withdrawing groups. The best enantioselectivities of 79–80% ee were achieved with heteroaromatic nitroalkenes (Ar = 2-furyl, 2-thiophenyl).

9. Enantioselective lanthanide-catalyzed hydroamination reactions

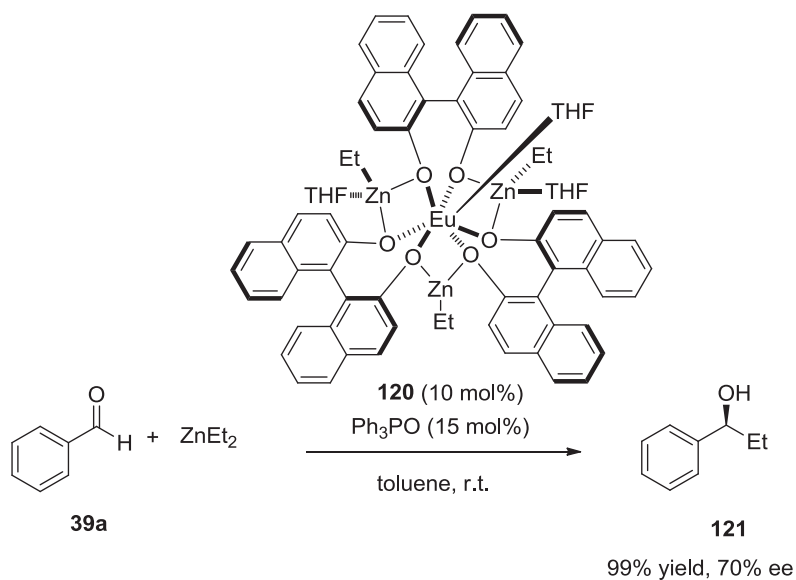
Hydroamination, consisting in the addition of an amine N–H bond to an unsaturated carbon–carbon bond, is of great potential

interest for the synthesis of nitrogen heterocycles that are found in numerous biologically active products. Consequently, it is not surprising that recent efforts have focused on the development of chiral catalysts for asymmetric alkene hydroamination [74]. Among them, chiral lanthanide catalysts have been proved to be promising for this transformation, enabling the synthesis of chiral amines in a single step. The first example was reported in 1992, using C_1 -symmetric chiral *ansa*-lanthanocene catalysts, that provided chiral pyrrolidines in up to 74% ee through intramolecular hydroamination [75]. Ever since, various chiral lanthanide complexes often based on biaryl ligands have been successfully applied to intra- and intermolecular asymmetric hydroaminations. The highest enantioselectivity achieved to date is 95% ee, and was obtained by using sterically hindered yttrium binaphtholate complexes [76]. Recently, several other examples have been reported, such as that reported by Hultzsich and Reznichenko, dealing with asymmetric lutetium-catalyzed intramolecular hydroamination of aminoalkenes **130a–e** into the corresponding cyclic chiral amines **131a–e** ([Scheme 44](#)) [77]. The reaction was promoted by novel

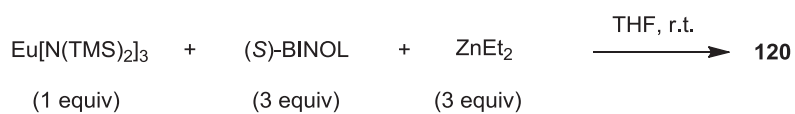


$R^1 = \text{Ph}, p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-BrC}_6\text{H}_4, p\text{-F}_3\text{CC}_6\text{H}_4, p\text{-PhC}_6\text{H}_4, p\text{-MeOC}_6\text{H}_4, p\text{-Tol}, m\text{-Tol}, o\text{-Tol}, 3,5\text{-Me}_2\text{C}_6\text{H}_3, 2\text{-Naph}, \text{Me}, \text{Bn}$
 $R^2 = \text{Ph}, p\text{-FC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4, p\text{-Tol}, p\text{-MeO}_2\text{CC}_6\text{H}_4, \text{BnCH}_2$

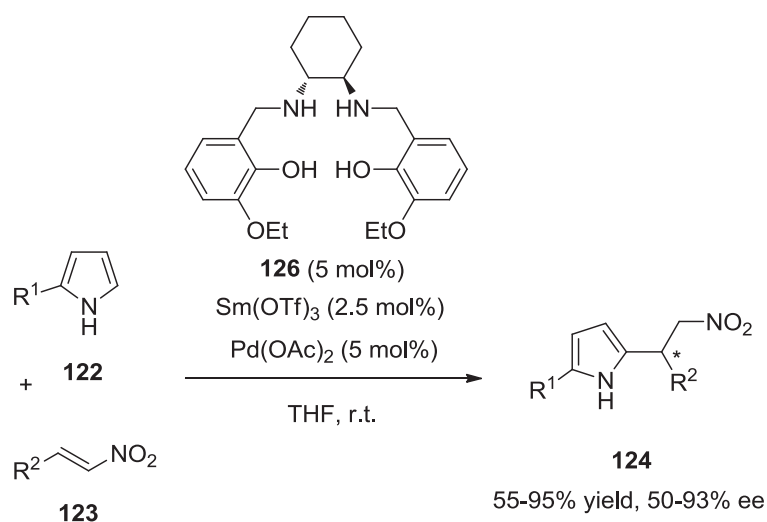
Scheme 40. Scandium-catalyzed addition of 3,3-dimethylindolin-2-one to 2*H*-azirines through kinetic resolution [66].



preparation of catalyst **120**:



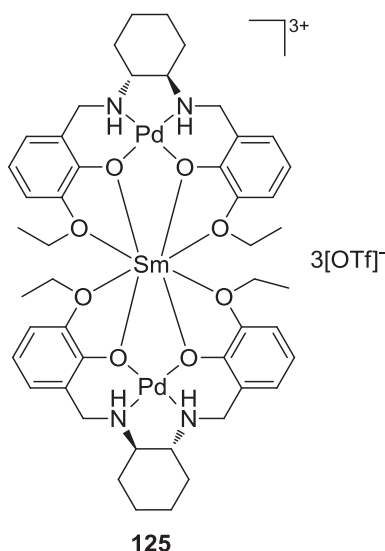
Scheme 41. Addition of ZnEt₂ to benzaldehyde promoted by heterobimetallic Eu/Zn/BINOL complex [67].



R¹ = H, Et

R² = Ph, *p*-FC₆H₄, *p*-ClC₆H₄, *p*-BrC₆H₄, *p*-MeOC₆H₄, 2-furyl,
 2-thiophenyl, *n*-Bu

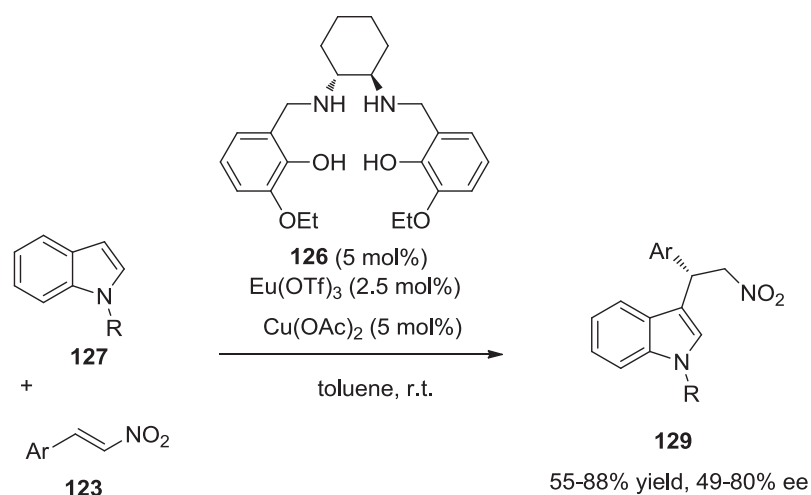
structure for active catalyst **125**:



Scheme 42. Friedel–Crafts reaction of pyrroles with nitroalkenes promoted by heterotrimeric Pd/Sm/Pd complex [70].

C₁-symmetric aminodiolate lutetium complexes in situ generated from 1.4 to 2 mol% of the corresponding chiral ligands **132** or **133**, and the same quantity of [Lu(*o*-C₆H₄CH₂NMe₂)₃] as precatalyst. The NOBIN-derived aminodiolate ligands **132–133** featured sterically demanding triphenylsilyl *ortho* substituent on the naphtholate moiety and hindered substituents, such as *tert*-butyl (for **132**) and triphenylsilyl (for **133**), on the phenolate moiety. When the reaction was performed with ligand **132**, it provided five-membered (bicyclic) products **131a–b** in moderate enantioselectivities (52–62%), six-membered product **131c** with the highest enantioselectivity (73% ee) while seven-membered product **131d** was formed in lower enantioselectivity (27% ee). Aminopentene **130e** (*n* = 1, R³ = H) also led to the corresponding product **131e** in 66% ee by using ligand **133**. In all cases, the products were formed with an excellent conversion of >95%.

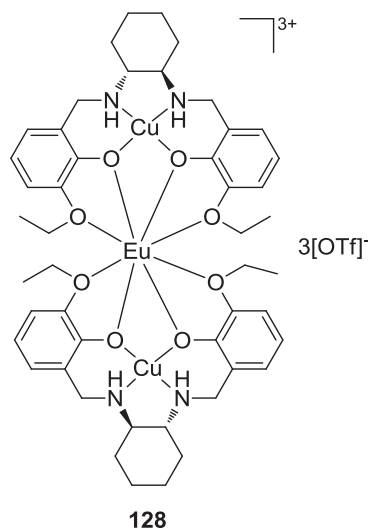
On the basis of the precedent results obtained in asymmetric lutetium-catalyzed intramolecular hydroaminations, the same group investigated the intermolecular version between alkenes **134a–b** and benzylamine **135** [76]. However, in this case better enantioselectivities (36–40% ee vs 7–9% ee) were achieved for the formed corresponding chiral amines **136a–b** by using the corresponding yttrium precatalyst instead of the lutetium one. As shown in Scheme 45, the reaction was performed in the presence of ligand **133** or **137** and [Y(*o*-C₆H₄CH₂NMe₂)₃] as precatalyst, providing products **136a–b** in both moderate yields (52–62%) and enantioselectivities (36–40% ee). According to the NMR spectra of lutetium and yttrium complexes involved in reactions depicted in Schemes 44 and 45, the monomeric unsymmetric structure shown in Scheme 45 was proposed for the active catalysts.



R = H, Me

Ar = Ph, *p*-FC₆H₄, *p*-ClC₆H₄, *p*-BrC₆H₄, *p*-MeOC₆H₄, 2-furyl, 2-thiophenyl

structure for active catalyst **128**:



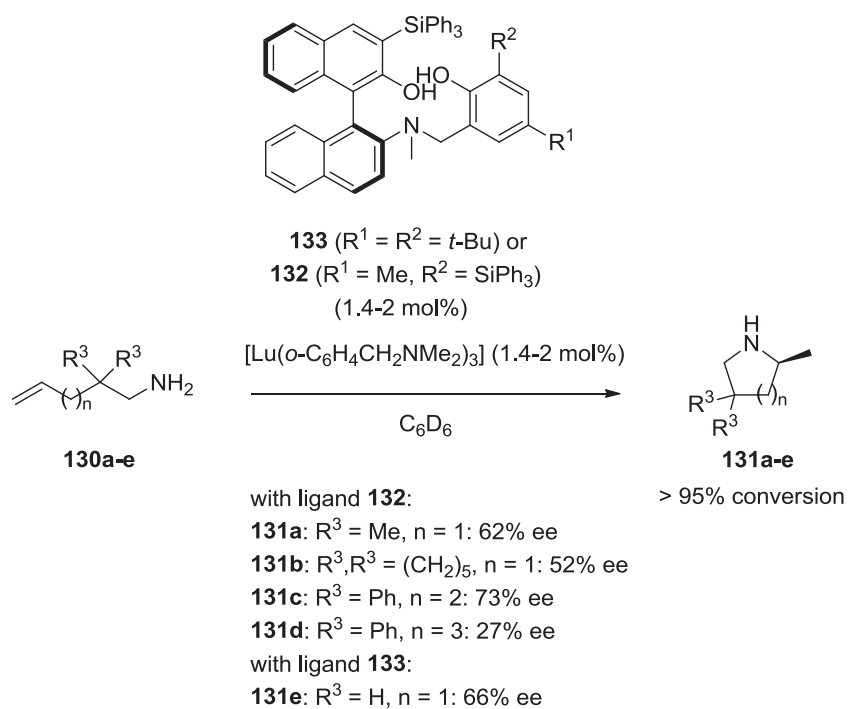
Scheme 43. Friedel-Crafts reaction of indoles with nitroalkenes promoted by heterotrimeric Cu/Eu/Cu complex [72].

The asymmetric intramolecular hydroamination of alkenes **130a–b,f** into the corresponding cyclic chiral amines **131a–b,f** was also investigated by Roesky et al. by using chiral *N,N'*-bis-(1-phenylethyl)benzamidine **138** as ligand [78]. As shown in Scheme 46, the corresponding novel preformed yttrium and lutetium catalysts **139** and **140** were prepared in C₆D₆ at 100 °C, the structures of which were characterized through X-ray diffraction. The use of yttrium complex **139** allowed product **131f** to be obtained at room temperature in 96% yield and 66% ee while the catalysis by lutetium complex **140**, performed at room temperature or 60 °C, provided products **131a–b** in excellent yields (92–100%) and good enantioselectivities (69–75% ee).

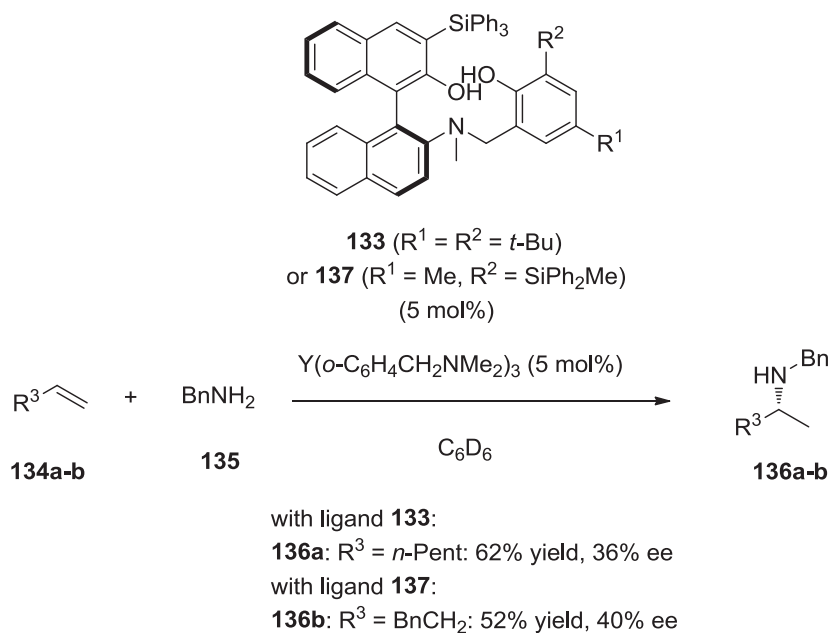
10. Enantioselective lanthanide-catalyzed ring-opening reactions

The nucleophilic ring-opening of epoxides represents an important strategy in organic synthesis because of its powerful capability

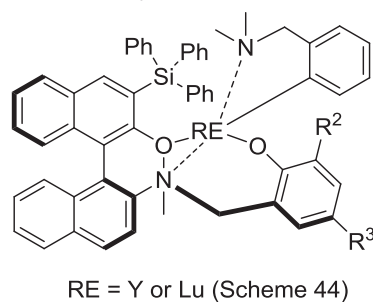
in forming bonds [79]. This process leads to the possible formation of two adjacent stereocenters at the α,α' -positions of the *meso*-epoxide, allowing chiral 1,2-difunctional compounds, including 1,2-diol monoethers, 1,2-amino alcohols, or 1,2-thioalcohols, to be easily synthesized. In the past decade, lanthanide complexes of chiral bipyridine or chiral *N,N'*-dioxide ligands have been successfully applied to the ring-opening reactions of *meso*-epoxides with a variety of nucleophiles, such as alcohols, amines, including *N*-heterocycles and indoles, as well as thiols [80]. In contrast to the wide variety of compatible nucleophiles, the usual substituent of the *meso*-epoxides is commonly either an alkyl or an aryl group, for example, *cis*-cycloalkane or *cis*-stilbene. However, these approaches remain limited when a carbonyl group is situated at the α -position of the epoxide. In this context, Wang et al. recently investigated the first asymmetric lanthanide-catalyzed ring-opening of *meso*-diketoepoxides **141a–m** with 2-mercaptobenzothiazoles **142a–j** [81]. Among a range of lanthanide triflates, including scandium, lanthanum, yttrium, and gadolinium



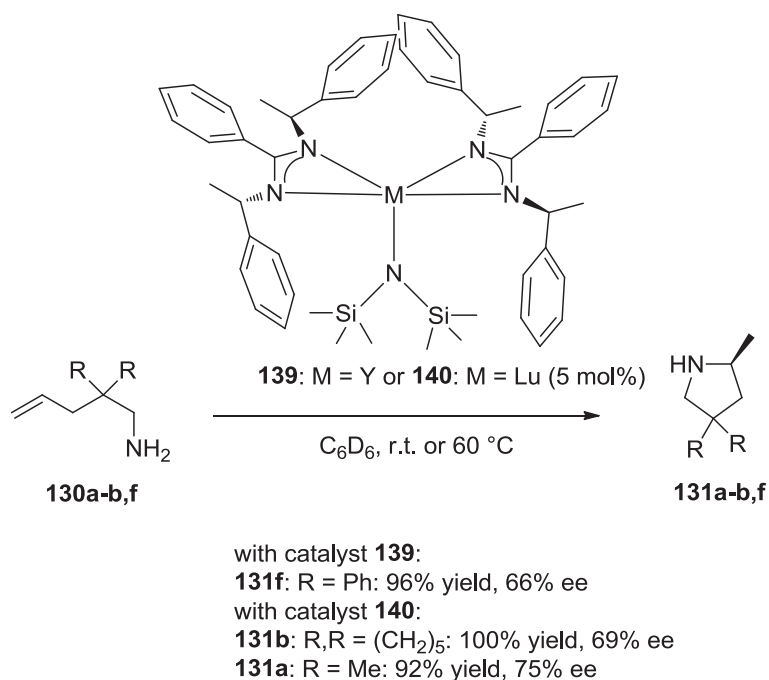
Scheme 44. Lutetium-catalyzed intramolecular hydroamination of alkenes [76].



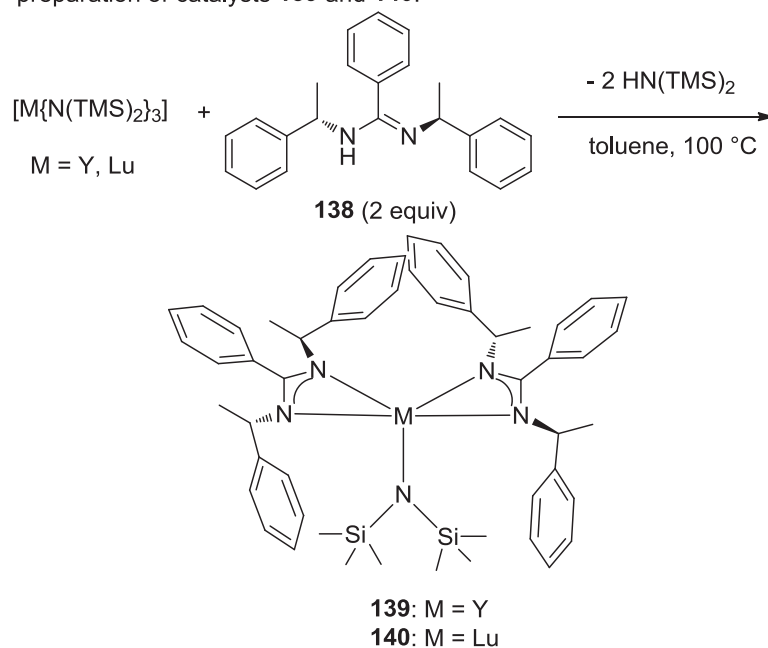
supposed structure of active catalyst:



Scheme 45. Yttrium-catalyzed intermolecular hydroamination of alkenes [76].



preparation of catalysts **139** and **140**:

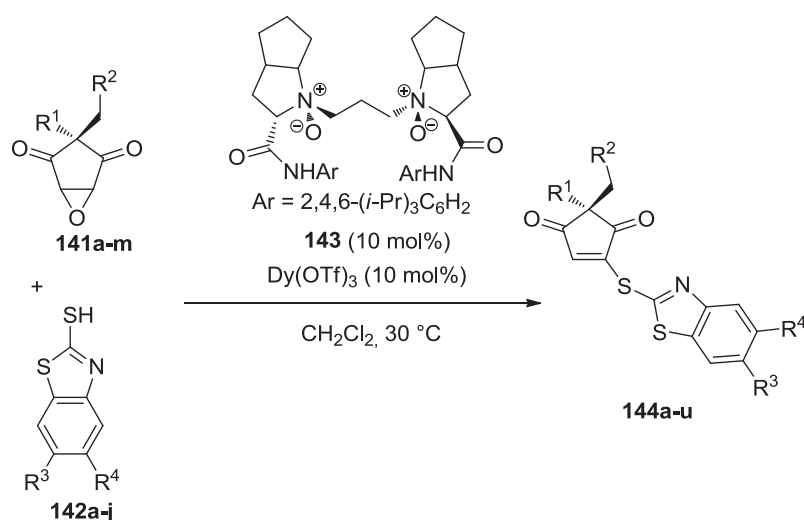


Scheme 46. Yttrium and lutetium-catalyzed intramolecular hydroamination of alkenes [77].

ones, Dy(OTf)₃ was found optimal when combined to chiral *N,N'*-dioxide ligand **143** in dichloromethane at 30 °C. Indeed, when the reaction was performed with 10 mol% of this catalyst system, it led to the corresponding chiral functionalized cyclopentene-1,3-diones **144a-u** in uniformly high yields (81–99%) and enantioselectivities (90–94% ee), as shown in [Scheme 47](#). Notably, the substitution pattern of both the two substrates almost had no effect on the yield and enantioselectivity of the reaction. Since a number of biologically important compounds contain cyclopentene-1,3-dione units, this novel methodology will play an important role in the near future.

Earlier in 2014, Parquette and RajanBabu reported the synthesis of novel bimetallic yttrium catalyst **146** which was further applied

to promote the asymmetric ring-opening of *N*-acylaziridines, such as **145a**, with silyl isothiocyanates **147a-e** [82]. As shown in [Scheme 48](#), the reaction led to the corresponding thiocyanate products **148a-e** in moderate to almost quantitative yields and moderate enantioselectivities of up to 69% ee. The substituents (R¹,R²) on the silicon atom in the silyl isothiocyanate had a significant effect on the enantioselectivity of the reaction since the highest ee values were achieved in the case of bulky substrates **148b,d-e**. With the aim of increasing these enantioselectivities, the same reactions were performed in the presence of a related bimetallic catalyst **149** which actually provided comparable results (≤68% ee, [Scheme 48](#)). The ring-opening of racemic substituted *N*-acylaziridines **150a-f** with TMSN₃ was also studied in the



- 144a:** R¹ = Me, R² = Ph, R³ = R⁴ = H: 96% yield, 93% ee
144b: R¹ = Me, R² = Ph, R³ = H, R⁴ = OMe, : 92% yield, 94% ee
144c: R¹ = Me, R² = Ph, R³ = H, R⁴ = Cl: 87% yield, 90% ee
144d: R¹ = Me, R² = Ph, R³ = H, R⁴ = OEt: 93% yield, 92% ee
144e: R¹ = R⁴ = Me, R² = Ph, R³ = Br: 97% yield, 90% ee
144f: R¹ = R³ = Me, R² = Ph, R⁴ = H: 94% yield, 93% ee
144g: R¹ = Me, R² = Ph, R³ = Cl, R⁴ = H: 81% yield, 92% ee
144h: R¹ = R⁴ = Me, R² = Ph, R³ = H: 97% yield, 94% ee
144i: R¹ = Et, R² = Ph, R³ = R⁴ = H: 97% yield, 92% ee
144j: R¹ = Me, R² = *o*-BrC₆H₄, R³ = R⁴ = H: 95% yield, 93% ee
144k: R¹ = Me, R² = *m*-BrC₆H₄, R³ = R⁴ = H: 94% yield, 92% ee
144l: R¹ = Me, R² = *p*-F₃CC₆H₄, R³ = R⁴ = H: 92% yield, 90% ee
144m: R¹ = Me, R² = *m*-ClC₆H₄, R³ = R⁴ = H: 95% yield, 92% ee
144n: R¹ = Me, R² = *o*-Tol, R³ = R⁴ = H: 99% yield, 92% ee
144o: R¹ = Me, R² = *m*-Tol, R³ = R⁴ = H: 99% yield, 94% ee
144p: R¹ = Me, R² = *p*-Tol, R³ = R⁴ = H: 98% yield, 92% ee
144q: R¹ = Me, R² = 1-Naph, R³ = R⁴ = H: 93% yield, 92% ee
144r: R¹ = Me, R² = 2-Naph, R³ = R⁴ = H: 97% yield, 92% ee
144s: R¹ = Me, R² = CH₂=CH, R³ = R⁴ = H: 92% yield, 90% ee
144t: R¹ = Me, R² = Et, R³ = R⁴ = H: 99% yield, 94% ee
144u: R¹ = R² = Me, R³ = R⁴ = H: 97% yield, 90% ee

Scheme 47. Dysprosium-catalyzed ring-opening of *meso*-diketooxepoxides with 2-mercaptobenzothiazoles [80].

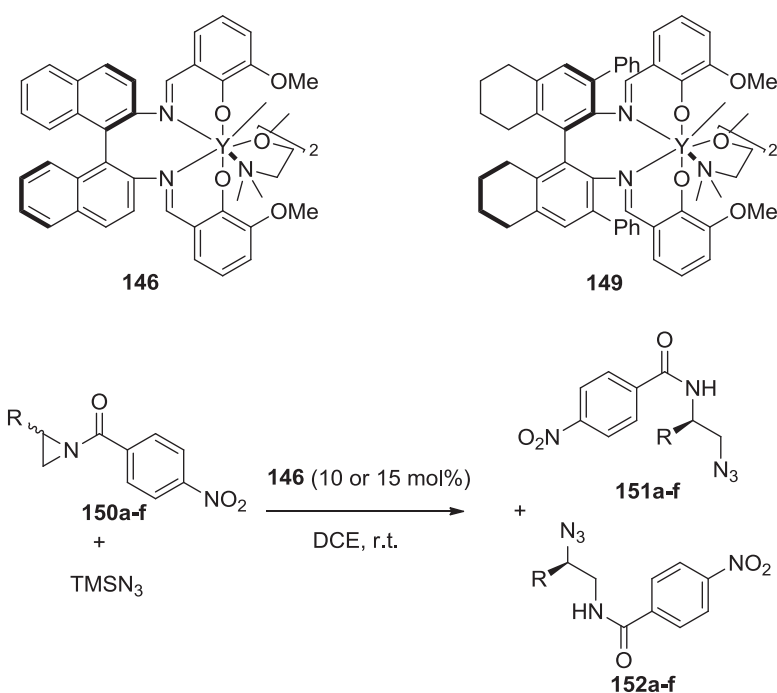
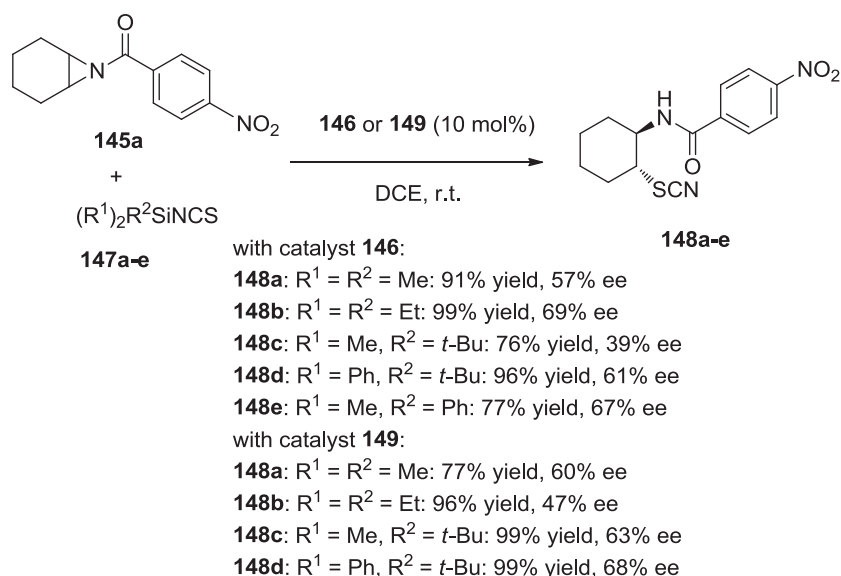
presence of dimeric yttrium-salen catalyst **146** in DCE. The reaction allowed the formation of a mixture of two regioisomeric ring-opened products **151a–f** and **152a–f** to be achieved in excellent enantioselectivities of up to 99% ee, as shown in [Scheme 48](#). The nucleophilic attack by azide occurred exclusively at the primary position in (*R*)-aziridines **150a–f**, leading to chiral azido-amides **151a–f** as single products. In contrast, (*S*)-aziridines **150a–f** yielded the corresponding products **152a–f**, resulting from an exclusive S_N2-inversion at the secondary center. The scope of the process was extended to a range of structurally different substituted *N*-acylaziridines **150a–f** which all reacted enantiospecifically, producing primary azides **151a–f** derived from (*R*)-enantiomers of aziridines in 99% ee in each case. The selectivities in the formation of products **152a–f** derived from (*S*)-enantiomers of aziridines were also excellent, since enantioselectivities of 90–99% ee were obtained in most cases. Slightly lower enantioselectivities of 90–93% ee were obtained for aziridines **150d–f** bearing *n*-butyl, isopropyl, and cyclohexylmethyl

substituents (R). These reactions were also performed by using a monometallic yttrium catalyst bearing a related ligand, but they were much less selective since moderate enantioselectivities of 54–77% ee were obtained for the two products. The remarkable enantioselectivities obtained by using bimetallic catalyst **146** indicated that a bimetallic activation in which both the aziridine and the nucleophile (N₃) were activated thus looked plausible. This study represented the first regiodivergent parallel kinetic resolution of racemic monosubstituted aziridines upon reaction with TMSN₃.

11. Enantioselective lanthanide-catalyzed domino and tandem reactions

11.1. Scandium catalysts

A domino reaction was defined by Tietze as a process involving two or more bond-forming transformations which take place

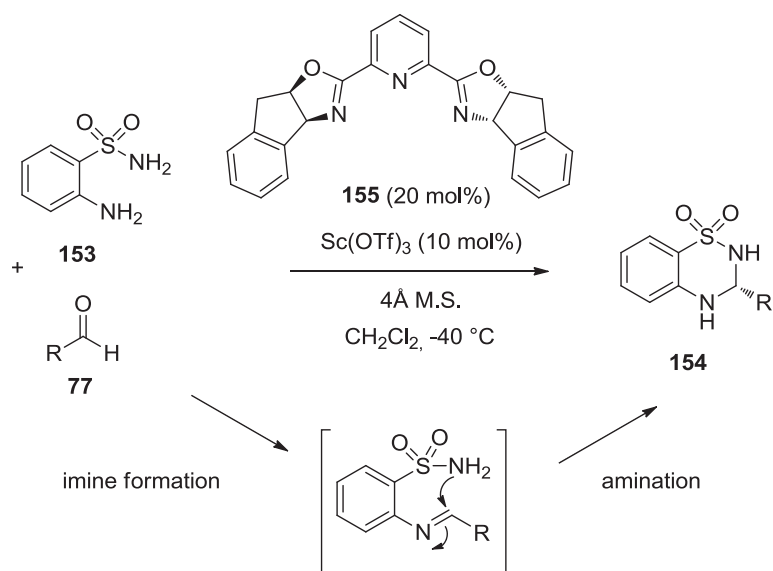


$R = \text{Cy}$: 42% yield (**151a**), > 99% ee (**151a**), 46% yield (**152a**), 99% ee (**152a**)
 $R = c\text{-Pent}$: 33% yield (**151b**), > 99% ee (**151b**), 39% yield (**152b**), 98% ee (**152b**)
 $R = \text{Bn}$: 42% yield (**151c**), 99% ee (**151c**), 47% yield (**152c**), 97% ee (**152c**)
 $R = n\text{-Bu}$: 32% yield (**151d**), 99% ee (**151d**), 48% yield (**152d**), 90% ee (**152d**)
 $R = i\text{-Pr}$: 16% yield (**151e**), 99% ee (**151e**), 48% yield (**152e**), 92% ee (**152e**)
 $R = \text{CyCH}_2$: 15% yield (**151f**), > 99% ee (**151f**), 51% yield (**152f**), 93% ee (**152f**)

Scheme 48. Yttrium-catalyzed ring-opening reactions of *N*-acylaziridines with silyl isothiocyanates and $TMSN_3$ [81].

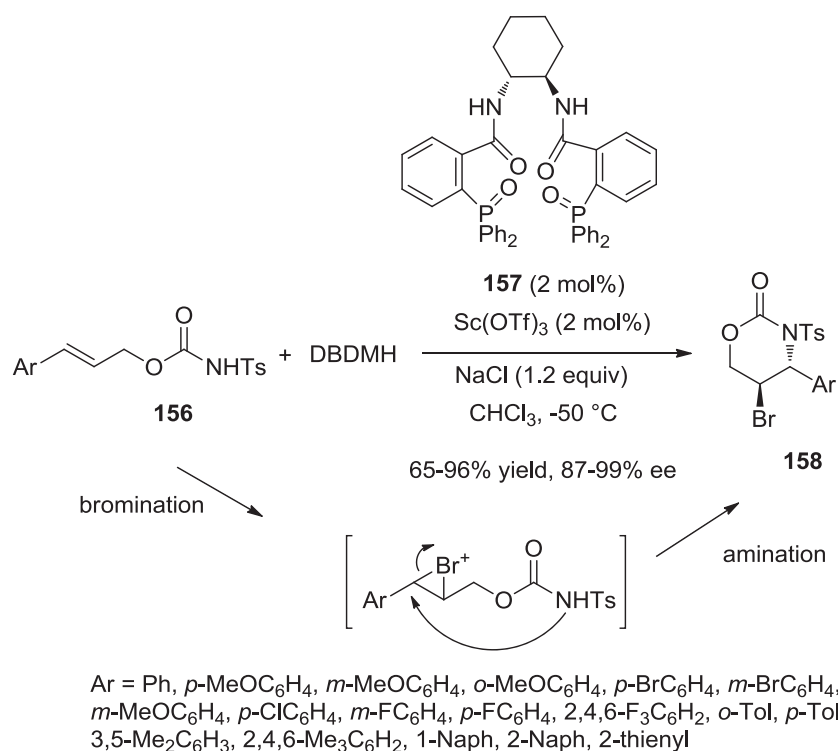
under the same reaction conditions, without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed by bond formation or fragmentation in the previous step [83]. The use of these one-pot reactions is increasing constantly [84], and had already allowed the synthesis of a wide range of complex natural and/or biologically important molecules [85], avoiding costly and time-consuming protection-deprotection processes, as well as purification procedures of intermediates [86]. In the past decade, a number of chiral scandium catalysts have been successfully applied to

various asymmetric domino reactions including multicomponent ones, such as three-component Mannich-type reactions [87], three-component aza-Diels-Alder reactions [88], and three-component allylation reactions [89] among others. A more recent example was reported by Zhou et al., dealing with asymmetric domino imine formation/intramolecular amination reaction of aldehydes **77** with 2-aminobenzenesulfonamide **153** to yield the corresponding chiral 3,4-dihydro-2*H*-1,2,4-benzothiadiazine-1,1-dioxides **154** [90]. These products constitute an important class of substances with a wide range of biological activities. As shown



with R = *i*-Bu, *i*-Pr, *t*-BuCH₂, Cy, *c*-Pent, *c*-Pr, Bn, BnCH₂:
 60-75% yield, 73-92% ee
 with R = Ph, *p*-MeOC₆H₄, *p*-BrC₆H₄, *m*-BrC₆H₄, *o*-BrC₆H₄,
 3-Br-4-MeOC₆H₃, 1-furyl:
 60-88% yield, 36-93% ee

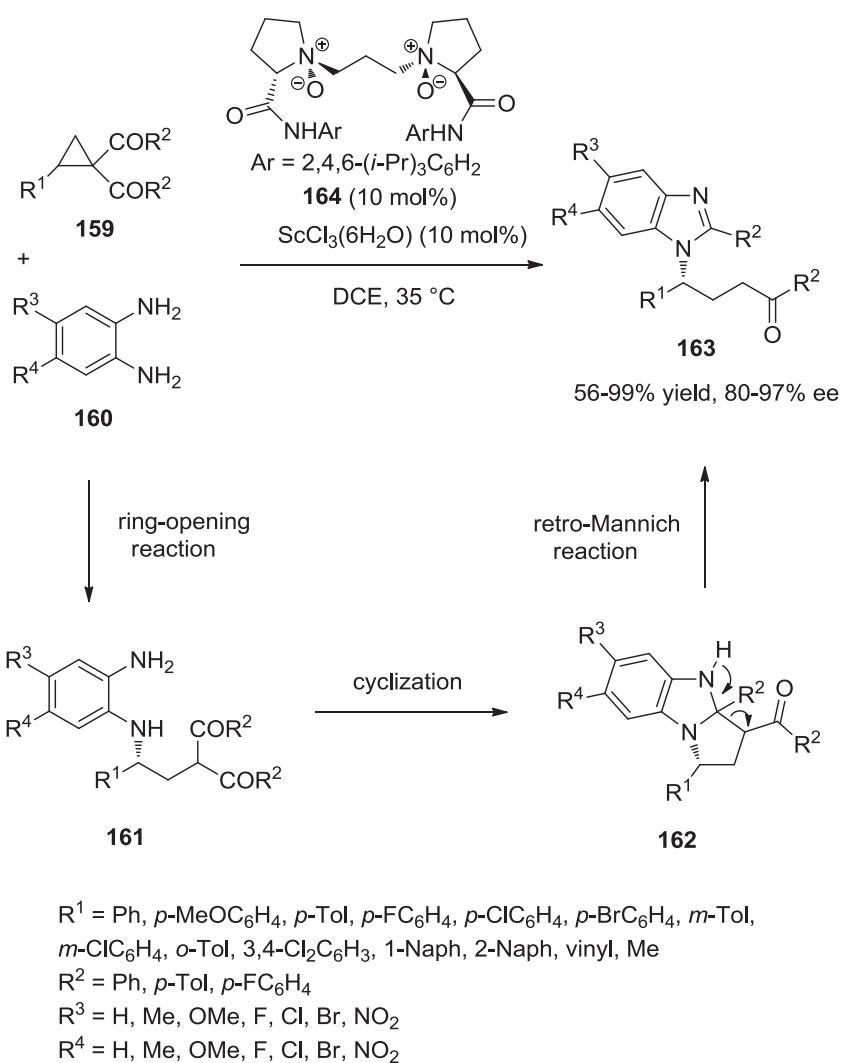
Scheme 49. Scandium-catalyzed domino imine formation/intramolecular amination reaction of aldehydes with 2-aminobenzenesulfonamide [89].



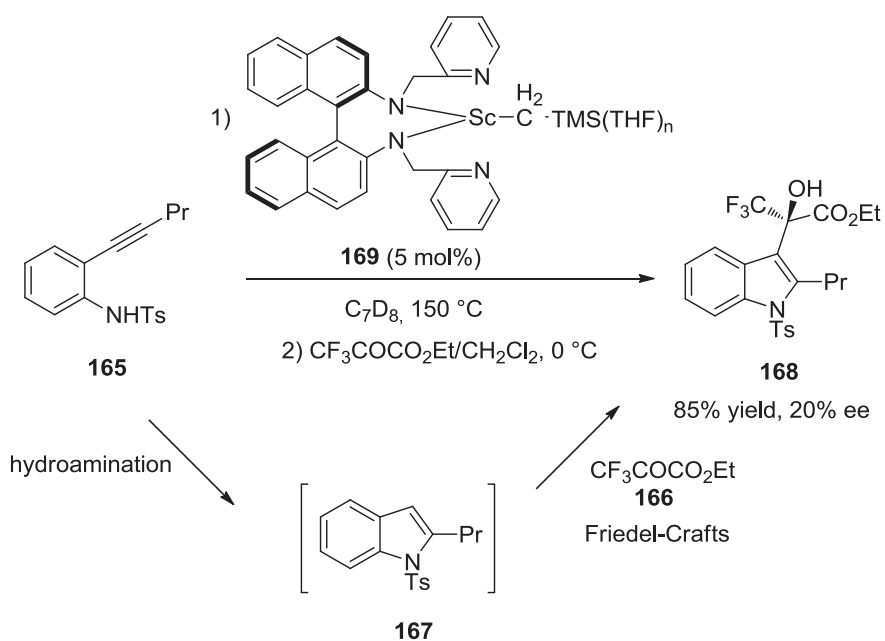
Scheme 50. Scandium-catalyzed domino bromination/amination reaction of (*E*)-cinnamyl tosylcarbamates [90].

in [Scheme 49](#), when the reaction was performed in dichloromethane at -40°C with a combination of 10 mol% of $\text{Sc}(\text{OTf})_3$ as precatalyst, and 20 mol% of chiral *inda*-Pybox ligand **155**, it provided a range of 3-alkyl- or 3-aryl-substituted chiral 3,4-dihydro-2*H*-1,2,4-benzothiadiazine-1,1-dioxides **154** in moderate to high

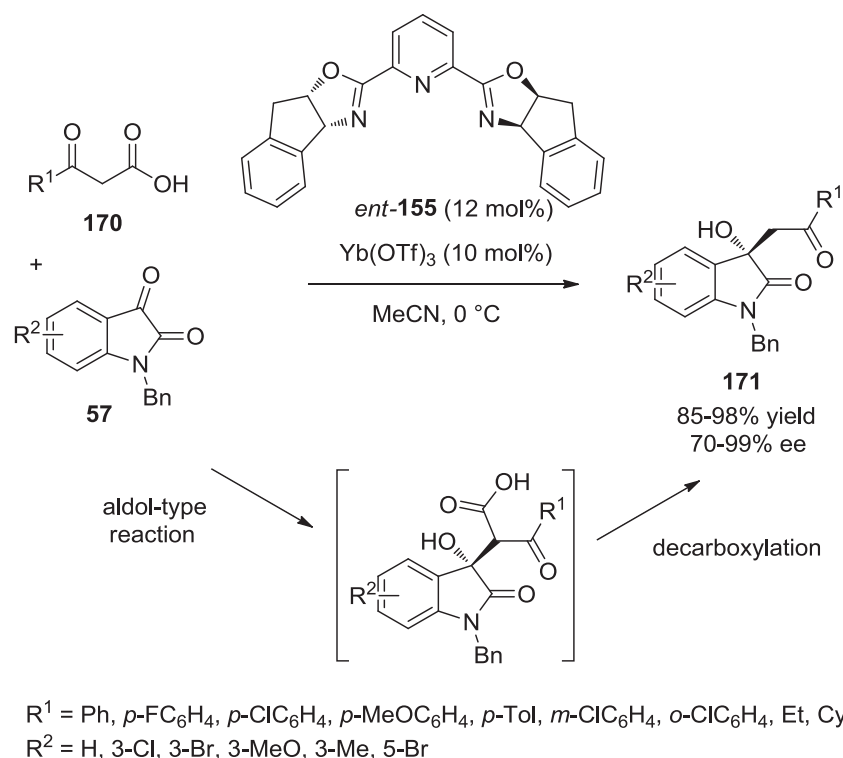
yields (60–88%) and enantioselectivities (36–93% ee). The best enantioselectivities (73–92% ee) were generally obtained for aliphatic aldehydes while aromatic ones provided low to high enantioselectivities (36–93% ee). This novel efficient methodology was supposed to evolve through intermolecular imine formation



Scheme 51. Scandium-catalyzed domino ring-opening/cyclization/retro-Mannich reaction of cyclopropyl ketones with aryl 1,2-diamines [91].



Scheme 52. Scandium-catalyzed tandem hydroamination/Friedel-Crafts reaction of an aniline derivative with ethyl 3,3,3-trifluoropyruvate [92].



Scheme 53. Ytterbium-catalyzed domino aldol/decarboxylation reaction of isatins with β -ketoacids [93].

followed by intramolecular asymmetric amine addition to give the final product (Scheme 49).

The same year, Shi et al. reported highly regio- and enantioselective scandium-catalyzed domino bromination/amination reaction of (*E*)-cinnamyl tosylcarbamates **156** with 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) as the bromine source [91]. As shown in Scheme 50, the reaction was performed in chloroform at $-50\text{ }^\circ\text{C}$ with NaCl as superstoichiometric additive and employed a scandium catalyst in situ generated from 2 mol% of $\text{Sc}(\text{OTf})_3$, and 2 mol% of chiral phosphine oxide **157** as ligand. Under these reaction conditions, a range of chiral aryl 5-bromo-1,3-oxazin-2-ones **158** were produced in good to excellent yields (65–96%) and uniformly high enantioselectivities (87–99% ee). The aryl groups (Ar) could be *ortho*-, *meta*-, and *para*-substituted. Furthermore, mono, di- as well as tri-substituted aryl groups were well tolerated. Even naphthalene and thiophene-substituted substrates provided excellent results (89–99% ee). The resulting halides could be easily converted into highly versatile synthetic intermediates.

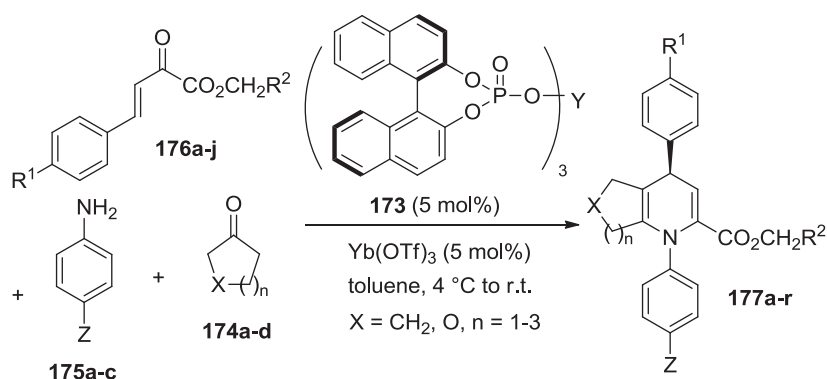
Benzimidazoles are ubiquitously found in natural products and bioactive compounds. In 2016, Liu and Feng described the first asymmetric route to these products based on an enantioselective scandium-catalyzed domino ring-opening/cyclization/*retro*-Mannich reaction of cyclopropyl ketones **159** with aryl 1,2-diamines **160** [92]. As shown in Scheme 51, the process began with the ring-opening of the cyclopropane substrate **159** by the diamine **160** to give the corresponding ring-opened intermediate **161** which subsequently underwent cyclization to form tricyclic intermediate **162**. The latter was further submitted to a *retro*-Mannich reaction to afford the final benzimidazole **163** bearing a chiral side chain. When the reaction was catalyzed in DCE at $35\text{ }^\circ\text{C}$ with a combination of 10 mol% of $\text{ScCl}_3(6\text{H}_2\text{O})$, and the same quantity of chiral *N,N'*-dioxide ligand **164**, products **163** were obtained in good to quantitative yields (56–99%) and high enantioselectivities (80–97% ee). The reaction was suitable to a variety of cyclopropyl ketones with either electron-poor- or electron-rich-substituted

aryl groups (80–95% ee) as well as naphthyl-substituted substrates (92–93% ee). Notably, even a vinyl-substituted cyclopropane was also compatible, thus producing the corresponding product in 90% ee and 86% yield.

In addition, Hannedouche et al. recently developed the asymmetric scandium-catalyzed tandem hydroamination/Friedel–Crafts reaction of aniline derivative **165** with ethyl 3,3,3-trifluoropyruvate **166** [93]. The process began with an intramolecular hydroamination to give intermediate **167** which further reacted with ethyl 3,3,3-trifluoropyruvate **166** through a Friedel–Crafts alkylation, affording final indole **168**. The use of 5 mol% of novel preformed scandium catalyst **169** in this process allowed obtaining a good yield (85%) albeit combined with a low enantioselectivity (20% ee), as shown in Scheme 52.

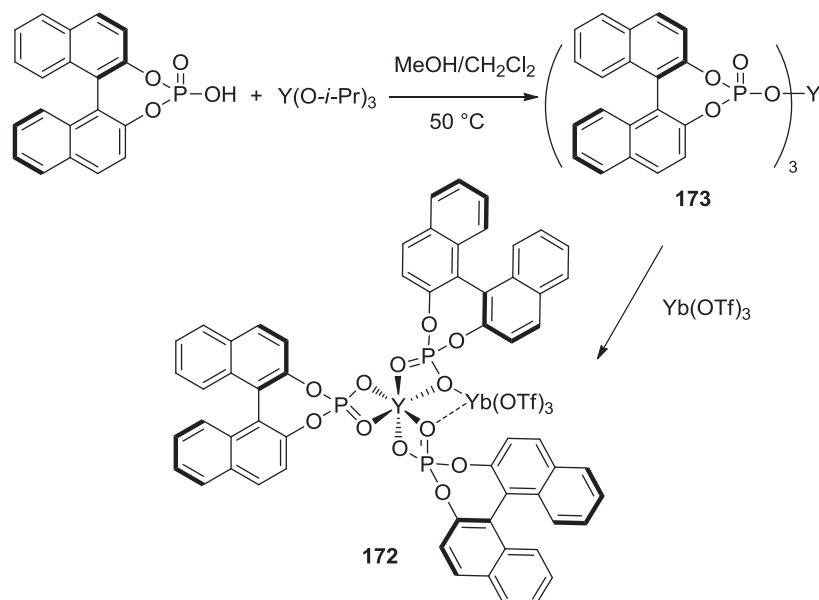
11.2. Other catalysts

In the last few years, several types of enantioselective domino reactions have been successfully catalyzed by chiral ytterbium complexes. For example, Wang et al. developed ytterbium-catalyzed asymmetric domino aldol/decarboxylation reaction of isatins **57** with β -ketoacids **170**, in 2013 [94]. Among several Pybox ligands investigated along with $\text{Yb}(\text{OTf})_3$ as precatalyst, chiral *inda*-Pybox ligand *ent*-**155** was found optimal at 12 mol% of catalyst loading in acetonitrile at $0\text{ }^\circ\text{C}$ to afford the corresponding biologically important 3-hydroxy-3-substituted chiral oxindoles **171**. As shown in Scheme 53, these products were obtained in uniformly high yields (85–98%) combined with good to excellent enantioselectivities (70–99% ee) through successive aldol-type reaction between the two substrates and decarboxylation. A variety of isatin derivatives with different substituents were compatible. The protecting group on the nitrogen showed a crucial influence on the reactivity of electrophiles. Without any protecting group, isatin reacted to give the desired domino product in a high yield (90%) albeit with a much lower enantioselectivity (27% ee vs 99% ee).



- 177a:** X = CH₂, Z = OMe, R¹ = Cl, R² = Ph, n = 1: 70% yield, 82% ee
177b: X = CH₂, Z = OMe, R¹ = Cl, R² = Me, n = 1: 74% yield, 82% ee
177c: X = CH₂, Z = OMe, R¹ = Br, R² = Ph, n = 1: 77% yield, 84% ee
177d: X = CH₂, Z = OMe, R¹ = F, R² = Ph, n = 1: 79% yield, 85% ee
177e: X = CH₂, Z = R¹ = OMe, R² = Ph, n = 1: 75% yield, 89% ee
177f: X = CH₂, Z = R¹ = OMe, R² = Me, n = 1: 78% yield, 88% ee
177g: X = CH₂, Z = OMe, R¹ = F, R² = Me, n = 1: 69% yield, 83% ee
177h: X = CH₂, Z = Cl, R¹ = OMe, R² = Ph, n = 1: 66% yield, 63% ee
177i: X = CH₂, Z = OMe, R¹ = R² = Me, n = 3: 78% yield, 81% ee
177j: X = CH₂, Z = R¹ = OMe, R² = Me, n = 3: 74% yield, 89% ee
177k: X = CH₂, Z = R¹ = OMe, R² = Ph, n = 3: 71% yield, 87% ee
177l: X = CH₂, Z = OMe, R¹ = Cl, R² = Ph, n = 3: 80% yield, 80% ee
177m: X = CH₂, Z = OMe, R¹ = F, R² = Me, n = 3: 79% yield, 84% ee
177n: X = CH₂, Z = OMe, R¹ = Br, R² = Me, n = 3: 75% yield, 85% ee
177o: X = CH₂, Z = H, R¹ = F, R² = Me, n = 3: 70% yield, 84% ee
177p: X = CH₂, Z = Cl, R¹ = OMe, R² = Ph, n = 3: 63% yield, 60% ee
177q: X = CH₂, Z = OMe, R¹ = Cl, R² = Ph, n = 2: 94% yield, 91% ee
177r: X = O, Z = OMe, R¹ = Cl, R² = Me, n = 2: 80% yield, 70% ee

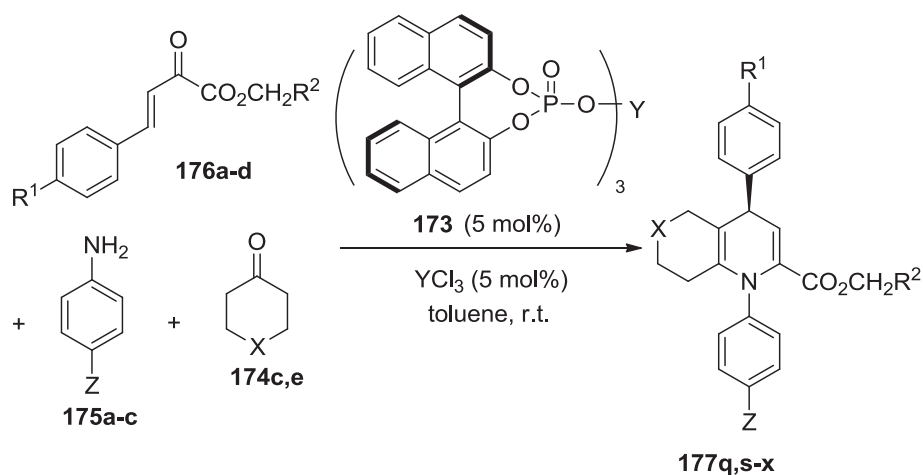
preparation of active complex **172**:



Scheme 54. Three-component reaction of cyclic ketones, arylamines, and β,γ -unsaturated α -ketoesters catalyzed by heterobimetallic $\text{Yb}/\text{Y}/\mathbf{173}$ complex [94].

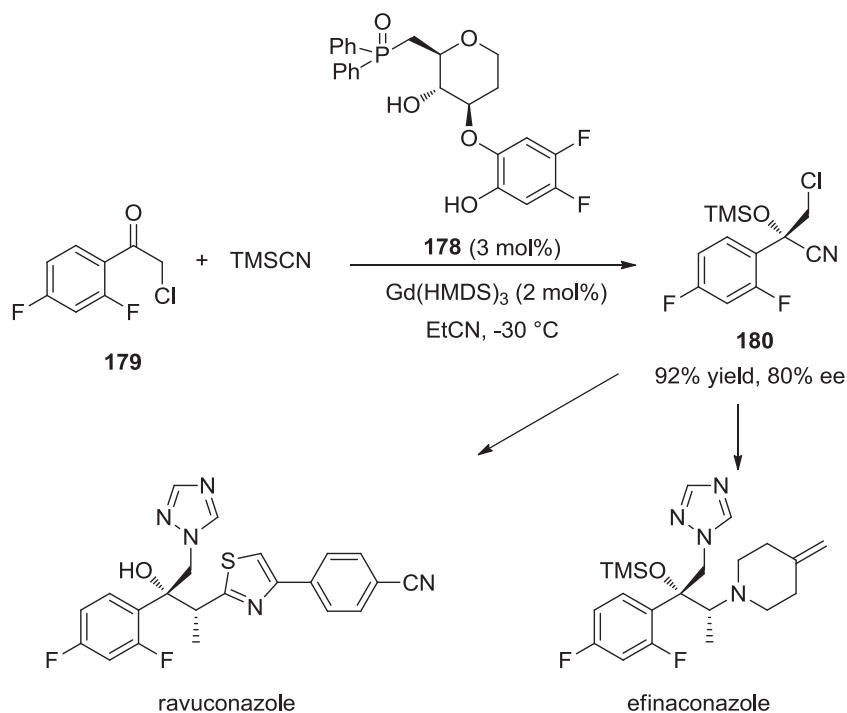
Sterically hindered protecting groups, such as Boc and triphenylmethyl, also led to low enantioselectivities (0–33% ee). Actually, the best results were achieved with *N*-benzyl isatins. Different sub-

stituents (R²) on the aromatic ring of isatin **57** were tolerated but substitution at the 6-position with electron-donating or electron-withdrawing groups afforded consistently high yields (88–98%),



- 177q:** X = CH₂, Z = OMe, R¹ = Cl, R² = Ph: 92% yield, 93% ee
177s: X = CH₂, Z = OMe, R¹ = R² = H: 89% yield, 93% ee
177t: X = CH₂, Z = OMe, R¹ = Cl, R² = H: 91% yield, 96% ee
177u: X = CH₂, Z = R¹ = OMe, R² = H: 86% yield, 96% ee
177v: X = CH₂, Z = R² = H, R¹ = Cl: 82% yield, 99% ee
177w: X = CH₂, Z = R¹ = Cl, R² = H: 79% yield, 96% ee
177x: X = S, Z = OMe, R¹ = Cl, R² = H: 89% yield, 93% ee

Scheme 55. Three-component reaction of cyclic ketones, arylamines, and β,γ -unsaturated α -ketoesters catalyzed by homobimetallic yttrium complex [94].

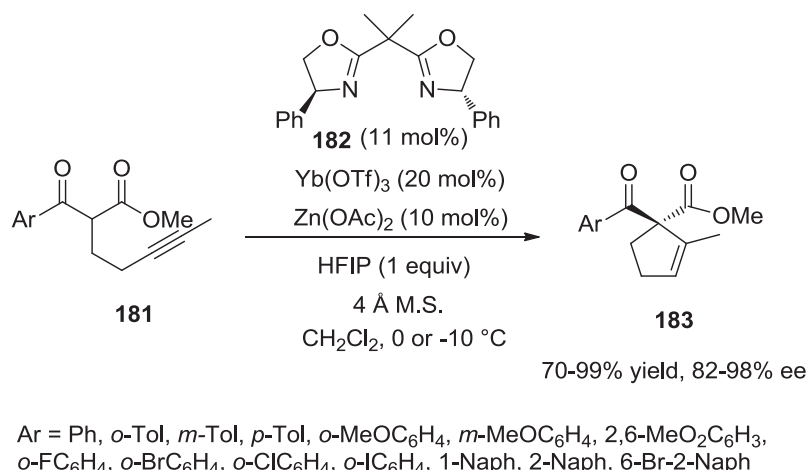


Scheme 56. Gadolinium-catalyzed cyanosilylation of a ketone, and synthesis of triazole antifungal agents [96].

and excellent enantioselectivities (98–99% ee). When 4-bromo isatin was employed, the enantioselectivity dropped to 65% ee, suggesting that the nucleophilic addition was inhibited by steric interference between the substituent at C4 and the metal/ligand complex. Furthermore, the scope of β -ketoacids **170** was found broad with the best results achieved in the case of aromatic β -ketoacids, with the exception of an *ortho*-chlorophenyl- β -

ketoacid (R¹ = *p*-ClC₆H₄) for which the ee value dropped to 70% ee. Notably, aliphatic β -ketoacids also reacted smoothly to give the corresponding products in excellent yields (88–93%) and good enantioselectivity (79% ee).

In 2015, Wang et al. reported the synthesis of a new type of chiral heterobimetallic Yb/Y catalyst **172** in situ generated from Yb(OTf)₃ and yttrium binaphthyl phosphate **173** (Scheme 54) [95].



Scheme 57. 5-*endo*-Dig cyclization of β -ketoesters with internal alkynes catalyzed by ytterbium and zinc catalysts [97].

The heterobimetallic structure of complex **172** was determined through ^1H and ^{13}P NMR and EPR spectroscopic studies as well as X-ray analysis. This catalyst was used to promote asymmetric three-component domino inverse-electron-demand/aza-Diels–Alder reactions of cyclic ketones **174a–d**. The use of cyclopentanone **174a** and cycloheptanone **174b** afforded novel biologically interesting chiral dihydropyridines containing 5/6 and 7/6 fused bicyclic rings. The reaction of cyclopentanone **174a** with arylamines **175a–c** and β,γ -unsaturated α -ketoesters **176a–j** afforded the corresponding aza-Diels–Alder products **177a–h** in 66–79% yields and high enantioselectivities of up to 89% ee. Concerning the reaction of cycloheptanone **174b**, β,γ -unsaturated α -ketoesters bearing both electron-donating and electron-withdrawing aromatic substituents at the γ -position reacted smoothly with *p*-methoxyaniline **175a**, providing products **177i–n** in 80–89% ee and 71–80% yields. When more electron-deficient *p*-chloroaniline **175b** ($Z = \text{Cl}$) was used, only moderate enantioselectivity of 60% ee was obtained for the corresponding product **177p** (Scheme 54). Furthermore, the reaction of cyclohexanone **174c** was also examined under these reaction conditions, providing the corresponding product **177q** in 94% yield and 91% ee. The conditions were also applicable to the formation of hetero-Diels–Alder product **177r** ($X = \text{O}$) in 80% yield and 70% ee.

In addition, replacing $\text{Yb}(\text{OTf})_3$ as precatalyst by YCl_3 allowed remarkable enantioselectivities of up to 99% ee to be achieved in the reactions of six-membered ketones **174c,e** with various enones **176a–d**, and arylamines **175a–c** to give the corresponding chiral products **177q,s–x** [94]. As shown in Scheme 55, the homobimetallic catalyst in situ generated from YCl_3 and chiral yttrium phosphate **173** displayed a general excellent activity (79–92% yields) as well as enantioselectivity (93–99% ee) for all substrates studied including heterofunctionalized ketone **174e** ($X = \text{S}$, product **177x**). Notably, this type of novel heterobimetallic or homobimetallic catalysts described in Schemes 54 and 55 was neither air- nor moisture-sensitive.

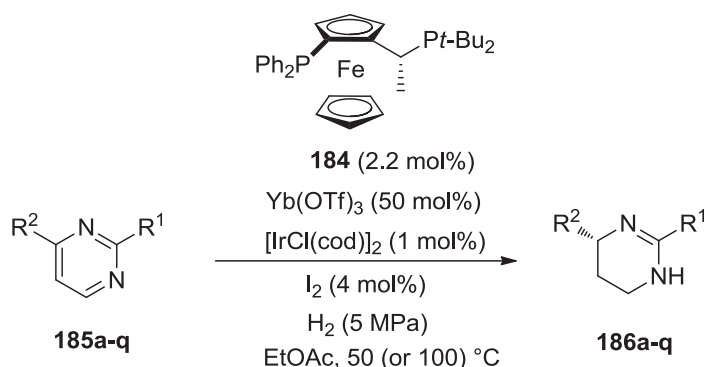
12. Miscellaneous enantioselective lanthanide-catalyzed reactions

The catalytic asymmetric cyanosilylation of aldehydes has been intensively studied with various chiral Lewis acids including lanthanide chiral catalysts [96], however, enantioselective catalytic cyanosilylations of ketones are more difficult owing to the lower reactivity of ketones compared to aldehydes. In 2014, Shibasaki

and Kumagai reported the use of a chiral gadolinium catalyst in situ generated from $\text{Gd}(\text{HMDS})_3$ and sugar-derived chiral ligand **178** to promote the enantioselective cyanosilylation of ketone **179** (Scheme 56) [97]. Performed in EtCN at -30°C in the presence of only 2–3 mol% of catalyst system, the process led to the corresponding chiral cyanohydrin **180** in high yield (92%) and good ee value (80% ee). This product was used as key intermediate in total syntheses of two triazole antifungal agents, such as ravuconazole, and efinaconazole (Scheme 56).

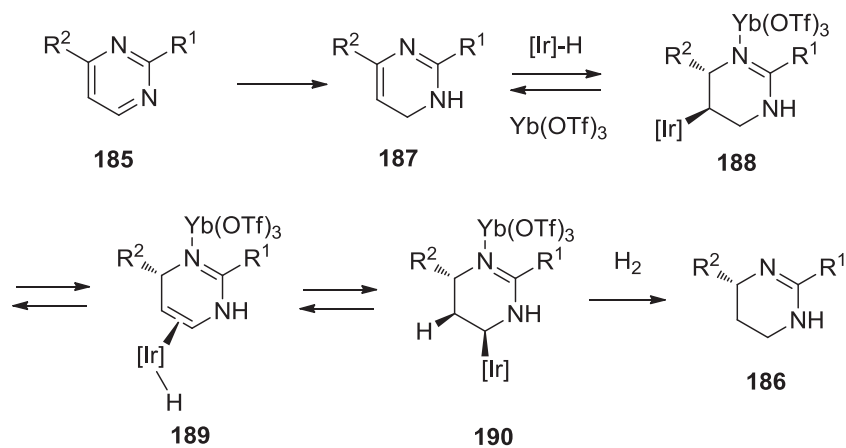
Earlier, Shibata et al. investigated the first enantioselective 5-*endo*-dig cyclization of β -ketoesters **181** with internal alkynes catalyzed by a combination of 20 mol% of $\text{Yb}(\text{OTf})_3$ and 10 mol% of $\text{Zn}(\text{OAc})_2$ in the presence of 11 mol% of chiral bisoxazoline **182** as ligand, and one equivalent of hexafluoroisopropyl alcohol (HFIP) as a stoichiometric additive (Scheme 57) [98]. Indeed, this four-component catalytic system was optimal to deliver the corresponding chiral *endo*-cyclized products **183** in good to quantitative yields (70–99%) and high enantioselectivities (82–98% ee). This protocol was equally compatible for a wide range of β -ketoesters **181**. Therefore, the results indicated that the nature of the substituents on the aryl group as well as their position had little effect on the yield and enantioselectivity of the reaction. The reaction of large aromatic 1- and 2-naphthyl substrates also provided the corresponding products in high enantioselectivities (82–95% ee). In this process, the role of $\text{Yb}(\text{OTf})_3$ was assumed to activate the alkyne moiety while the $\text{Zn}(\text{OAc})_2$ /**182** system was employed for the two-point binding of the dicarbonyl compound. The effect of HFIP was supposed to improve the catalytic turnover by protonation of a zinc–oxygen bond and subsequent release of the product from the transition state.

In another area, Kuwano et al. have developed asymmetric hydrogenation of pyrimidines catalyzed by a combination of ytterbium and iridium catalysts in the presence of ferrocene-containing chiral diphosphine ligand **184** [99]. Indeed, the combination of only 2.2 mol% of this ligand with 1 mol% of $[\text{IrCl}(\text{cod})_2]$ and 50 mol% of $\text{Yb}(\text{OTf})_3$ allowed the enantioselective hydrogenation of a range of 2,4-disubstituted pyrimidines **185a–q** into the corresponding chiral 1,4,5,6-tetrahydropyrimidines **186a–q** in good to quantitative yields (68–>99%) and enantioselectivities of up to 99% ee, as shown in Scheme 58. The enantioselectivity of the reaction was scarcely affected (86% ee for products **186a–b**) by the presence of *para* substituents on the 2-aryl groups (R^1). On the other hand, installing a substituent at the *ortho* position led to improvements in the enantioselectivity (87–95% ee for products **186c–f**). Cyclic amidines **186g–h** bearing a substituent ($R^2 = \text{Et}, \text{Cy}$) other than a



- 186a:** R¹ = *p*-F₃CC₆H₄, R² = Me: 87% yield, 86% ee
186b: R¹ = *p*-MeOC₆H₄, R² = Me: 93% yield, 86% ee
186c: R¹ = *o*-FC₆H₄, R² = Me: 92% yield, 92% ee
186d: R¹ = *o*-ClC₆H₄, R² = Me: 92% yield, 94% ee
186e: R¹ = *o*-Tol, R² = Me: 98% yield, 95% ee
186f: R¹ = *o*-MeOC₆H₄, R² = Me: 99% yield, 87% ee
186g: R¹ = *o*-Tol, R² = Et: > 99% yield, 96% ee
186h: R¹ = *o*-Tol, R² = Cy: 68% yield, 97% ee
186i: R¹ = R² = Ph: 92% yield, 97% ee
186j: R¹ = *o*-Tol, R² = Ph: 94% yield, 99% ee
186k: R¹ = *o*-Tol, R² = *p*-F₃CC₆H₄: 98% yield, 98% ee
186l: R¹ = *o*-Tol, R² = *p*-MeOC₆H₄: 98% yield, 99% ee
186m: R¹ = Ph, R² = CH₂OAc: 80% yield, 88% ee
186n: R¹ = *o*-Tol, R² = CF₃: 94% yield, 9% ee
186o: R¹ = *o*-Tol, R² = CO₂Et: 80% yield, 22% ee
186p: R¹ = Me, R² = Ph: 92% yield, 92% ee
186q: R¹ = NMe₂, R² = Ph: 87% yield, 91% ee (at 100 °C)

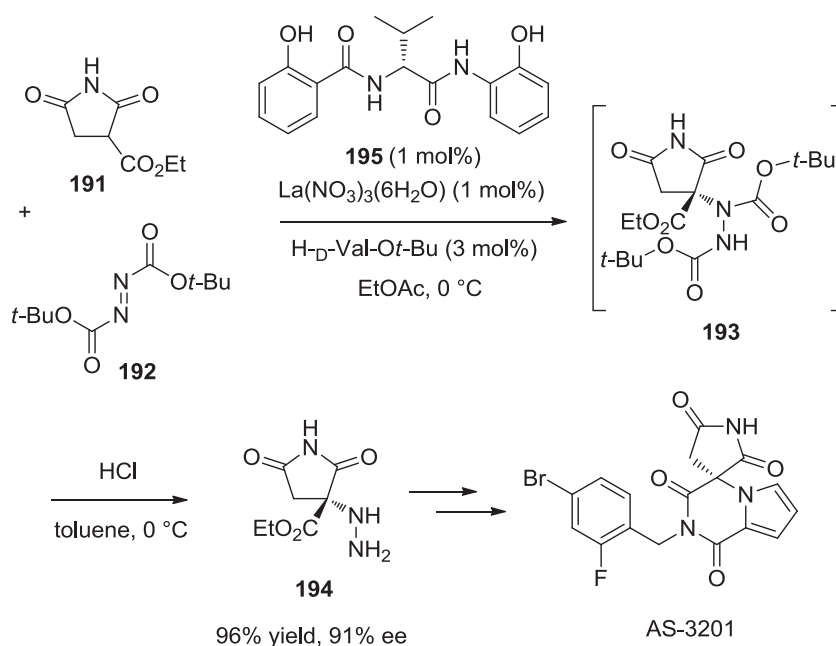
proposed pathway:



Scheme 58. Hydrogenation of pyrimidines catalyzed by ytterbium and iridium catalysts [98].

methyl group also underwent hydrogenation with high enantioselectivities (96–97% ee). In contrast, much lower enantioselectivities (9–22% ee) were obtained for pyrimidines **186n–o** bearing electron-withdrawing groups (R² = CF₃, CO₂Et). The hydrogenation protocol was also compatible with cyclic guanidine **185q** which led to the corresponding product **186q** in 91% ee albeit requiring a higher reaction temperature of 100 °C instead of 50 °C. The process

evolved through the pathway depicted in [Scheme 58](#) in which pyrimidine **185** was activated by coordination to Yb(OTf)₃. The N1–C6 bond of the substrate was then reduced with hydrogen to give dihydropyrimidine **187**. The C4–C5 double bond of **187** was inserted into the Ir–H bond to form intermediate **188**. The conversion of **188** into final product **186** proceeded through the migration of the iridium atom from C5 to C6. The Ir–C6 bond in intermediate



Scheme 59. Lanthanum-catalyzed amination of an imide, and synthesis of AS-3201 [100].

190 was protonated through σ -bond metathesis with hydrogen or through a sequence composed by an oxidative addition followed by a reductive elimination.

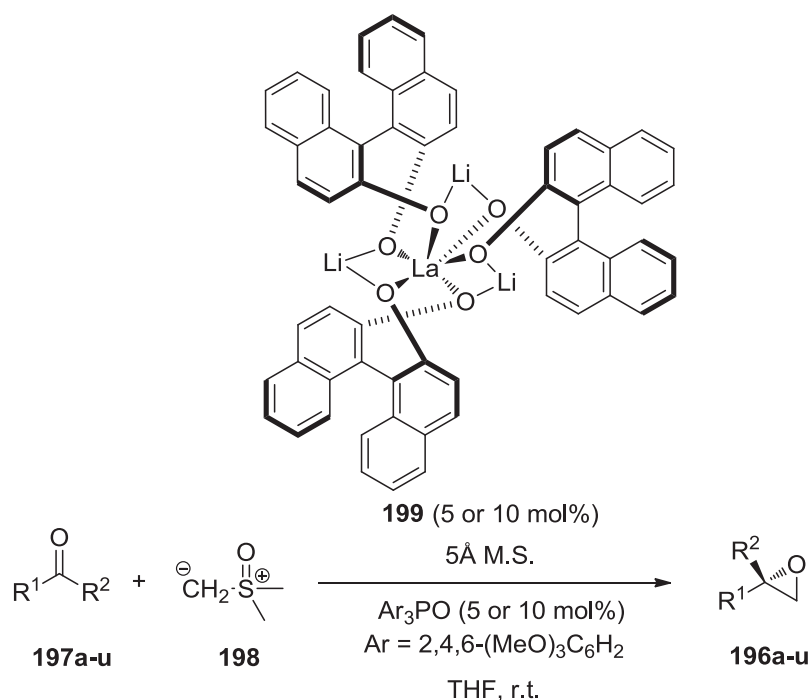
Early in 2007, Shibasaki et al. devised an elegant asymmetric lanthanum-catalyzed amination occurring between cyclic imide **191** and di-*t*-butylazodicarboxylate **192** to give the corresponding product **193** that was directly deprotected by treatment with HCl gas bubbling into toluene to provide final hydrazine **194** in 96% yield and 91% ee [100]. The latter constituted a key intermediate in the total synthesis of aldose reductase inhibitor AS-3201. In 2016, Bhogle et al. reported the first kilogram-scale application of this methodology performed in the presence of only 1 mol% of $\text{La}(\text{NO}_3)_3(6\text{H}_2\text{O})$ and the same quantity of chiral ligand **195** in ethyl acetate at 0 °C (Scheme 59) [101].

In 2012, an enantioselective synthesis of 2,2-disubstituted terminal epoxides **196a–u** was reported by Shibasaki et al. on the basis of a catalytic Corey–Chaykovsky epoxidation of the corresponding ketones **197a–u** with dimethyloxosulfonium methylide **198** (Scheme 60) [102]. A heterobimetallic La/Li/BINOL complex **199** was employed to promote the reaction, allowing a dual control of the two substrates by its double Lewis acidic moieties. The process proceeded smoothly at room temperature in the presence of an achiral sterically hindered aryl phosphine $\text{Ar}_3\text{P}=\text{O}$ ($\text{Ar} = 2,4,6\text{-(MeO)}_3\text{C}_6\text{H}_2$), providing 2,2-disubstituted terminal chiral epoxides **196a–m** in uniformly excellent enantioselectivities (91–96% ee) and yields (88–> 99%) starting from a broad range of methyl ketones **197a–m** ($\text{R}^2 = \text{Me}$) by using 5 mol% of catalyst loading. On the other hand, sterically more hindered ketones ($\text{R}^2 \neq \text{Me}$) resulted in lower enantioselectivities (67–88% ee) and required a higher catalyst loading of 10 mol%. Indeed, the enantioselectivity was strongly dependent on the steric hindrance of the ketones, and aryl ethyl ketones **197n–s** led to products **196n–s** in moderate to good ee values ($\leq 88\%$ ee), while ketones **197t–u** with bulkier substituents provided enantioselectivities $\leq 73\%$ ee.

Very recently, Lin and Feng reported the first enantioselective [3+3] annulation of cyclopropanes **200a–m** with mercaptoacetaldehyde **201** to give the corresponding chiral tetrahydrothiopyranols **202a–m** [103]. This was achieved by promoting the process at

50 °C with 10 mol% of a chiral scandium catalyst in situ generated from $\text{Sc}(\text{OTf})_3$ and chiral *N,N'*-dioxide ligand **203** in 1,1,2,2-tetrachloroethane (TCE) as solvent. As shown in Scheme 61, a number of aromatic substituted cyclopropyl ketones **200a–m** could undergo the reaction, providing the corresponding products in moderate to high yields (38–80%) and good to excellent diastereo- and enantioselectivities (78–>90% de and 84–99% ee, respectively). The electronic effect of the substituents on the aromatic Ar^1 group had an obvious influence on both the reactivity and enantioselectivity. Indeed, while an electron-donating methyl substituent at the *meta*-position of the phenyl group had no influence on the reactivity and enantioselectivity (product **202c**), when the methyl group was at the *ortho*- or *para*-position, the corresponding products **202b,d** were obtained in lower enantioselectivities (86–89% ee). Meanwhile, electron-withdrawing substituents caused a somewhat decrease of the yields, but the enantioselectivity and diastereoselectivity were still excellent (97–99% ee for products **202e–j**). Naphthyl-substituted cyclopropylketones were also compatible although the 1-naphthyl-substituted substrate **201k** led to the corresponding tetrahydrothiopyranol **202k** in much lower yield (38% vs 74%) and stereoselectivities (78% de vs 88% de and 84% ee vs 96% ee) than the 2-naphthyl-substituted cyclopropylketone **201l**.

In 2016, Vidal-Ferran et al. investigated the effect of lanthanide triflates as regulator agents, such as $\text{La}(\text{OTf})_3$ and $\text{Ho}(\text{OTf})_3$, to enhance the catalytic properties of palladium complexes derived from chiral biphosphite ligands and $[\text{Pd}(\mu\text{-Cl})(\eta^3\text{-C}_3\text{H}_5)_2]$ in asymmetric allylic substitutions [104]. Indeed, the addition of 5.5 mol% of these lanthanide triflates led to positive effects on the enantioselectivity (by up to 16% ee) for the asymmetric allylic substitution of 1,3-diphenylallyl acetate **204** with a nitrogen nucleophile, such as benzylamine **135**, to give the corresponding chiral amine **205**. As shown in Scheme 62, when the reaction was performed with a chiral palladium catalyst derived from biphosphite ligand **206** with 5.5 mol% of $\text{La}(\text{OTf})_3$ or $\text{Ho}(\text{OTf})_3$ in dichloromethane at room temperature, product **205** was obtained with complete conversion and moderate enantioselectivity of 46% ee instead of 30% ee when carrying out the reaction without these lanthanide triflates.



with 5 mol% of **199**:

- 196a**: $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{Me}$: 98% yield, 96% ee
196b: $\text{R}^1 = 2\text{-Naph}$, $\text{R}^2 = \text{Me}$: 97% yield, 96% ee
196c: $\text{R}^1 = p\text{-ClC}_6\text{H}_4$, $\text{R}^2 = \text{Me}$: > 99% yield, 94% ee
196d: $\text{R}^1 = m\text{-ClC}_6\text{H}_4$, $\text{R}^2 = \text{Me}$: > 99% yield, 94% ee
196e: $\text{R}^1 = o\text{-ClC}_6\text{H}_4$, $\text{R}^2 = \text{Me}$: 96% yield, 95% ee
196f: $\text{R}^1 = p\text{-FC}_6\text{H}_4$, $\text{R}^2 = \text{Me}$: 94% yield, 97% ee
196g: $\text{R}^1 = p\text{-EtO}_2\text{CC}_6\text{H}_4$, $\text{R}^2 = \text{Me}$: 94% yield, 94% ee
196h: $\text{R}^1 = p\text{-Tol}$, $\text{R}^2 = \text{Me}$: 97% yield, 92% ee
196i: $\text{R}^1 = 3\text{-pyridyl}$, $\text{R}^2 = \text{Me}$: 97% yield, 92% ee
196j: $\text{R}^1 = \text{BnCH}_2$, $\text{R}^2 = \text{Me}$: 99% yield, 93% ee
196k: $\text{R}^1 = n\text{-Oct}$, $\text{R}^2 = \text{Me}$: > 99% yield, 93% ee
196l: $\text{R}^1 = \text{Cy}$, $\text{R}^2 = \text{Me}$: 88% yield, 96% ee
196m: $\text{R}^1 = \text{EtO}_2\text{C}(\text{CH}_2)_3$, $\text{R}^2 = \text{Me}$: > 99% yield, 91% ee

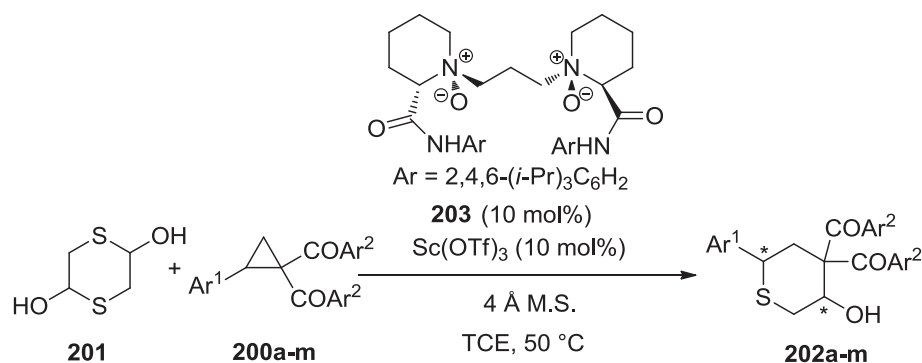
with 10 mol% of **199**:

- 196n**: $\text{R}^1 = \text{Ph}$, $\text{R}^2 = \text{Et}$: 91% yield, 88% ee
196o: $\text{R}^1 = p\text{-ClC}_6\text{H}_4$, $\text{R}^2 = \text{Et}$: 94% yield, 87% ee
196p: $\text{R}^1 = p\text{-BrC}_6\text{H}_4$, $\text{R}^2 = \text{Et}$: 92% yield, 85% ee
196q: $\text{R}^1 = m\text{-ClC}_6\text{H}_4$, $\text{R}^2 = \text{Et}$: 96% yield, 81% ee
196r: $\text{R}^1 = o\text{-FC}_6\text{H}_4$, $\text{R}^2 = \text{Et}$: 88% yield, 67% ee
196s: $\text{R}^1 = 3\text{-pyridyl}$, $\text{R}^2 = \text{Et}$: 89% yield, 73% ee
196t: $\text{R}^1 = p\text{-ClC}_6\text{H}_4$, $\text{R}^2 = n\text{-Pr}$: 90% yield, 73% ee
196u: $\text{R}^1 = \text{Ph}$, $\text{R}^2 = i\text{-Pr}$: 60% yield, 70% ee

Scheme 60. Epoxidation of ketones with dimethyloxosulfonium methylide catalyzed by heterobimetallic La/Li/BINOL complex [101].

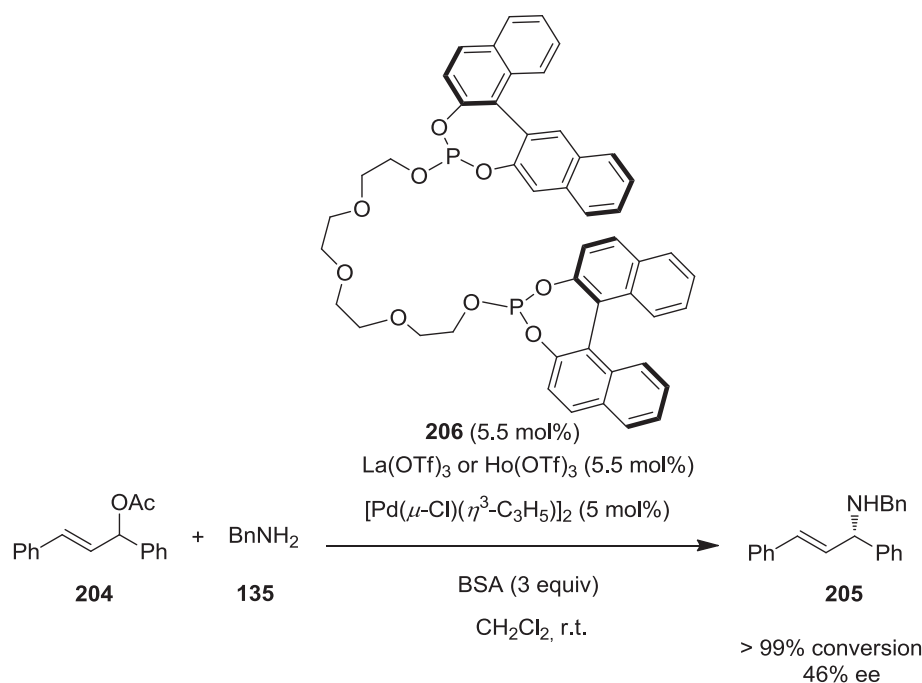
In addition, a related chiral biphosphite ligand **207** was used in combination with the same palladium precatalyst $[\text{Pd}(\mu\text{-Cl})(\eta^3\text{-C}_3\text{H}_5)]_2$ and $\text{La}(\text{OTf})_3$ to promote the asymmetric allylic alkylation of cinnamyl acetate **208** with dimethyl malonate **2a** [103]. As shown in **Scheme 63**, the reaction afforded a mixture of linear

product **210** and branched enantioenriched product **209** in 88:12 ratio with complete conversion. The enantioselectivity of minor product **209** was moderate (42% ee). Surprisingly, a higher enantioselectivity of 60% ee was achieved when performing the reaction in the absence of $\text{La}(\text{OTf})_3$ in contrast with the results observed in



- 202a:** Ar¹ = Ar² = Ph: 75% yield, 86% de, 97% ee
202b: Ar¹ = *o*-Tol, Ar² = Ph: 80% yield, > 90% de, 89% ee
202c: Ar¹ = *m*-Tol, Ar² = Ph: 76% yield, 88% de, 97% ee
202d: Ar¹ = *p*-Tol, Ar² = Ph: 72% yield, 88% de, 86% ee
202e: Ar¹ = *p*-FC₆H₄, Ar² = Ph: 56% yield, 86% de, 97% ee
202f: Ar¹ = *m*-ClC₆H₄, Ar² = Ph: 62% yield, 84% de, 98% ee
202g: Ar¹ = *p*-ClC₆H₄, Ar² = Ph: 51% yield, 86% de, 99% ee
202h: Ar¹ = 2,4-Cl₂C₆H₃, Ar² = Ph: 63% yield, 86% de, 99% ee
202i: Ar¹ = *m*-BrC₆H₄, Ar² = Ph: 50% yield, 86% de, 98% ee
202j: Ar¹ = *p*-BrC₆H₄, Ar² = Ph: 60% yield, 86% de, 99% ee
202k: Ar¹ = 1-Naph, Ar² = Ph: 38% yield, 78% de, 84% ee
202l: Ar¹ = 2-Naph, Ar² = Ph: 74% yield, 88% de, 96% ee
202m: Ar¹ = Ph, Ar² = *p*-Tol: 52% yield, 86% de, 97% ee

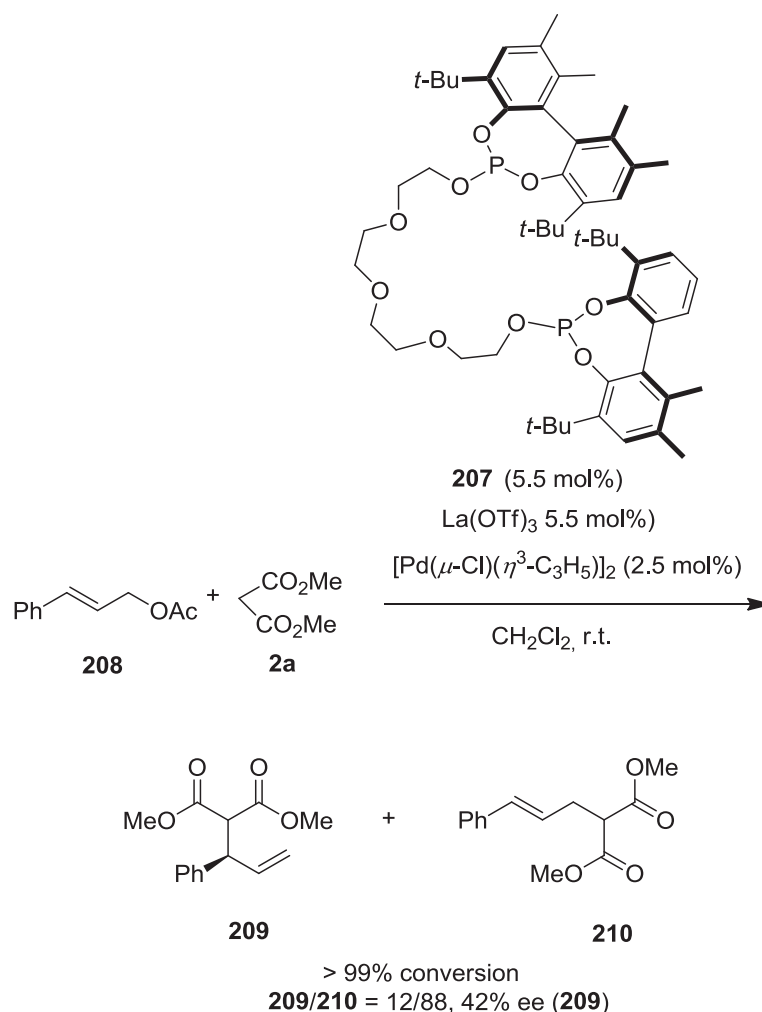
Scheme 61. Scandium-catalyzed [3+3] annulation of cyclopropanes with mercaptoacetaldehyde [102].



Scheme 62. Allylic amination of 1,3-diphenylallyl acetate with benzylamine promoted by palladium and lanthanum/holmium catalysts [103].

the asymmetric allylic amination of 1,3-diphenylallyl acetate **204** (Scheme 62) where the employment of a lanthanide triflate improved the enantioselectivity.

Finally, Roesky et al. recently synthesized and characterized through X-ray diffraction a novel heterogeneous manganese-, and gadolinium-containing one dimensional chiral coordination



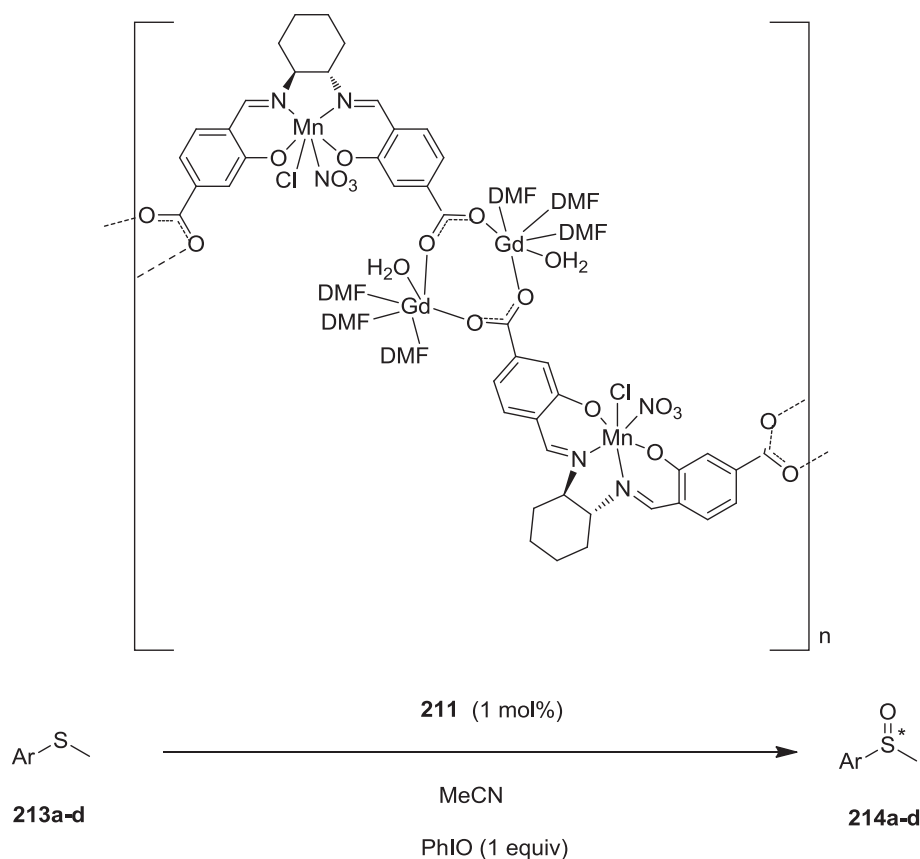
Scheme 63. Allylic alkylation of cinnamyl acetate with dimethyl malonate promoted by palladium and lanthanum catalysts [103].

polymer **211** from trivalent gadolinium nitrate Gd(NO₃)₃(H₂O)_n, manganese chloride MnCl₂(4H₂O), and chiral salen ligand **212** [105]. The polymer consisted of manganese–salen-based metalloligands having carboxylate linkers connected to gadolinium atoms forming the chiral one dimensional coordination polymer. This complex was investigated to promote the asymmetric oxidation of aryl sulfides **213a–d** with iodosobenzene into the corresponding sulfoxides **214a–d**. As shown in Scheme 64, these products were obtained in moderate to high conversions (36–78%) albeit with low enantioselectivities (3–25% ee). In spite of these low ee values, one advantage of this process was the use of only 1 mol% of a reusable catalyst.

13. Conclusions

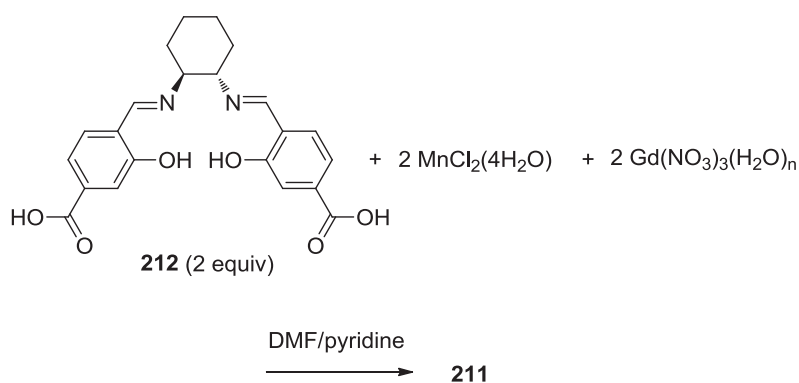
This review demonstrates that lanthanide enantioselective catalysis has gained growing interest to become indispensable in almost all spheres of organic transformations owing to the unique coordination properties of these special catalysts. Lanthanides are characterized by their ability to accommodate larger numbers of ligands than traditional metals, consequently, they are less prone to coordinative saturation, and allow the construction of structurally sophisticated complexes to be achieved. This rich and diverse coordination chemistry and the fact that lanthanide complexes do not possess stereoelectronic preferences for particular coordination geometries provide challenges for the development

of novel catalysts. This review updates the major progress reported since the beginning of 2012 in the field of all types of enantioselective transformations promoted by chiral lanthanide catalysts, illustrating the power of these special catalysts to provide a high degree of reactivity and stereoselectivity in a myriad of enantioselective transformations including highly efficient novel domino processes. It demonstrates that since the pioneering studies dealing with enantioselective europium-catalyzed hetero-Diels–Alder reactions reported by Danishefsky in 1983, a wide number of very different types of highly enantioselective lanthanide-catalyzed transformations have been developed with remarkable diversification outcomes. Among them, enantioselective Michael-type reactions have encountered wide success with, for example, the first asymmetric addition of malonates to α,β-unsaturated *N*-tosylimines developed by Blay and Pedro, using a chiral lanthanum catalyst that provided up to 92% ee. A rare example of enantioselective phospho-Michael addition was also recently reported by Xu, using an ytterbium–salen complex with 94% ee. Even higher enantioselectivities of up to 98–99% ee were achieved in enantioselective ytterbium-catalyzed Michael additions of 3-alkylidene oxindoles to chalcones reported by Feng, scandium-catalyzed Michael additions of malonates to enynes described by the same group, Michael additions of 1,3-dicarbonyl compounds to α,β-unsaturated ketones performed by Walsh, Pericas, and Schelter using a Shibasaki's type REMB heterobimetallic La/Na complex, and Michael additions of arylboronic acids to α,β-unsaturated amides developed by Kobayashi on the basis of a cooperative



214a: Ar = Ph: 78% conversion, 7% ee
214b: Ar = *p*-O₂NC₆H₄: 64% conversion, 25% ee
214c: Ar = *p*-NCC₆H₄: 71% conversion, 19% ee
214d: Ar = *p-n*-BuC₆H₄: 36% conversion, 3% ee

preparation of polymeric catalyst **211**:



Scheme 64. Oxidation of sulfides catalyzed by Mn/Gd polymeric catalyst [104].

catalysis with scandium and Rh/Ag nanoparticles. In the area of enantioselective cycloadditions, various chiral lanthanide complexes have also been successfully applied, such as a neodymium/*N,N*-dioxide ligand catalyst system developed by Feng, that provided up to 95% ee in enantioselective [3+2] cycloadditions of aldehydes with aziridines. Moreover, Pybox ligands were combined by Suga with lanthanum and lutetium to promote respectively 1,3-dipolar cycloadditions between *N*-diazoacetyl lactams with oxazolidinones with 95% ee, and 1,3-dipolar cycloadditions

between diazodiketones with indoles in up to >98% ee. Good results were also described in Diels–Alder cycloadditions with the involvement of a holmium catalyst derived from a chiral bistiourea by Nishida in the [4+2] cycloaddition of 3-[1-(silyloxy)vinyl]indole with *N*-acyloxazolidinones achieved with 94% ee. An interesting [2+2] photocycloaddition of enones was described by Yoon using a dual catalysis with europium and ruthenium, giving 97% ee. A range of excellent results were also published in the area of enantioselective lanthanide-catalyzed

aldol-type reactions. Among them, Walsh, Pericas, and Schelter developed direct aldol reactions with 95% ee when catalyzed by a heterobimetallic La/Li REMB-type catalyst. Very high enantioselectivities of 95–96% ee were also described by Allen in Mukaiyama-aldol reactions catalyzed by chiral neodymium and europium catalysts. Even higher enantioselectivities of 99% ee were achieved by Shibasaki in nitroaldol reactions based on heterobimetallic REMB-type catalysts. In the area of asymmetric epoxidations of alkenes, enantioselectivities of 97 and 99% ee were respectively reported by Tian and Zhao by using lanthanum and ytterbium chiral complexes. Remarkable enantioselectivities of 98–99% ee were described by Karimi and Shibasaki in Mannich reactions catalyzed by ytterbium and erbium chiral complexes. Furthermore, highly enantioselective 1,2-nucleophilic additions to carbonyl compounds and imines were reported, such as the first asymmetric addition of aldehydes to chromene acetals described by Rueping with 97% ee using a dual catalysis with ytterbium and an organocatalyst. Another excellent result was described by Liu and Feng with an enantioselective scandium-catalyzed 1,2-nucleophilic addition of azirines to 3,3-dimethylindolin-2-one with 99% ee. In another area, a rare example of Friedel–Crafts reaction of pyrroles with nitroalkenes was catalyzed by Zhang with a heterotrimetallic Pd/Sm/Pd complex with 93% ee, while Parquette and RajanBabu obtained >99% ee in ring-opening reactions of *N*-acylaziridines by using a bimetallic yttrium complex. Notably, a range of novel and uniformly high enantioselective domino processes have been very recently developed, such as scandium-catalyzed domino imine formation/intramolecular amination reactions of 2-aminobenzenesulfonamides reported by Zhou with 93% ee, scandium-catalyzed domino bromination/amination reactions of cinnamyl tosylcarbamates with 1,3-dibromo-5,5-dimethylhydantoin developed by Shi with 99% ee, and the first scandium-catalyzed domino ring-opening/cyclization/*retro*-Mannich reactions of cyclopropylketones with 1,2-diamines to give benzimidazoles with 97% ee reported by Liu and Feng. Chiral yttrium complexes also provided excellent results in domino reactions. For example, enantioselectivities of 99% ee were very recently reported by Wang in domino aldol/decarboxylation reactions of isatins with β -ketoacids or in three-component reactions between cyclic ketones, arylamines, and β,γ -unsaturated α -ketoesters. In addition, other types of transformations have provided remarkable enantioselectivities when catalyzed by various chiral lanthanide catalysts. For example, enantioselectivities of 98% ee were achieved by Shibata in enantioselective 5-*endo*-dig-cyclizations of β -ketoesters with internal alkynes by using a dual catalysis with yttrium and zinc. Kuwano has developed hydrogenation of pyrimidines into enantiopure 1,4,5,6-tetrahydropyrimidines catalyzed by a combination of yttrium and iridium. Shibasaki has also applied his heterobimetallic REMB-type complexes to the epoxidation of ketones with dimethyloxosulfonium methylide with 96% ee, while the first enantioselective [3+3] annulation between cyclopropanes and mercaptoacetaldehyde was reported by Lin and Feng on the basis of chiral scandium catalysis, providing 99% ee. Lanthanide Lewis acids present the particularity of being compatible with water in contrast to traditional Lewis acids which need strictly anhydrous conditions. Therefore, various lanthanide-catalyzed organic reactions can be performed not only in organic solvents but also in water. This will lead to more environmentally friendly reaction systems, and their applications in total synthesis in the near future.

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