

Recent applications of rare-earth metal(III) triflates in cycloaddition and cyclization reactions

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Abstract

Rare-earth metal(III) triflates are extremely mild, efficient and water-tolerable Lewis acid catalysts for a wide range of organic transformations. Rare-earth metal triflates retain activity even in the presence of multiple Lewis bases containing oxygen, nitrogen, sulfur and phosphorus atoms, and can be easily recovered and reused without any loss of catalytic activity. This review summarizes recent developments and highlights key applications of these unique Lewis acids in cycloaddition and cyclization reactions.

Keywords: Rare-earth triflates, lanthanide triflates, cyclization, cycloaddition, Lewis acid, catalysis

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1. Introduction

In the last two decades, the application of lanthanide triflates $\text{Ln}(\text{OTf})_3$ ($\text{Ln} = \text{La}, \text{Ce}, \text{Pr}, \text{Nd}, \text{Sm}, \text{Eu}, \text{Gd}, \text{Tb}, \text{Dy}, \text{Ho}, \text{Er}, \text{Tm}, \text{Yb}, \text{Lu}$; $\text{OTf} = \text{CF}_3\text{SO}_3^-$) in organic synthesis has experienced immense growth. Lanthanide(III) triflates, together with chemically similar triflates of pseudolanthanides $\text{Sc}(\text{III})$ and $\text{Y}(\text{III})$, have proven to be mild, stable Lewis acids that are known for their oxophilicity¹ and stability in the presence of water², making them water-compatible Lewis acids particularly suitable for green chemistry applications. These rare-earth metal(III) triflates $[\text{M}(\text{OTf})_3]$ remain active in the presence of a wide variety of Lewis bases, thereby providing exceptional functional group tolerance and in many cases obviating the need for protecting groups. $\text{M}(\text{OTf})_3$ have demonstrated high chemo- and regioselectivity, and exceptional conversions for a number of challenging synthetic transformations. Moreover, unlike traditional Lewis acids such as BF_3 , AlCl_3 , TiCl_4 , etc., catalytic usage, recovery and reuse are possible for $\text{M}(\text{OTf})_3$ reagents. Their low toxicity, environmentally benign character, moderate cost and ease of availability make these reagents attractive for the synthetic community. Intriguingly, a recent report demonstrated that lanthanides are an essential cofactor for methanol dehydrogenase in a volcanic methanotropic bacterium, thereby underscoring that lanthanides' superior catalytic properties are used in biological systems.³

Rare-earth elements(III) triflates are readily prepared from the corresponding oxides (M_2O_3) or chlorides (MCl_3) in an aqueous trifluoromethanesulfonic acid.^{4,5} Since their introduction into organic synthesis in 1987 by Frosberg and co-workers,⁶ and subsequent pioneering studies by Kobayashi's research group,⁷⁻⁹ the field of $\text{Sc}(\text{OTf})_3$, $\text{Y}(\text{OTf})_3$ and $\text{Ln}(\text{OTf})_3$ -catalyzed reactions has seen evergrowing interest with several reviews covering the major aspects of this chemistry published to date.¹⁰⁻¹⁵ Therefore, the purpose of the present review is not to summarize all the efforts in the area comprehensively, but instead highlight a select number of important applications of rare-earth metal triflates in cyclization and cycloaddition reactions reported over the last five years, up to the first three quarters of 2013.

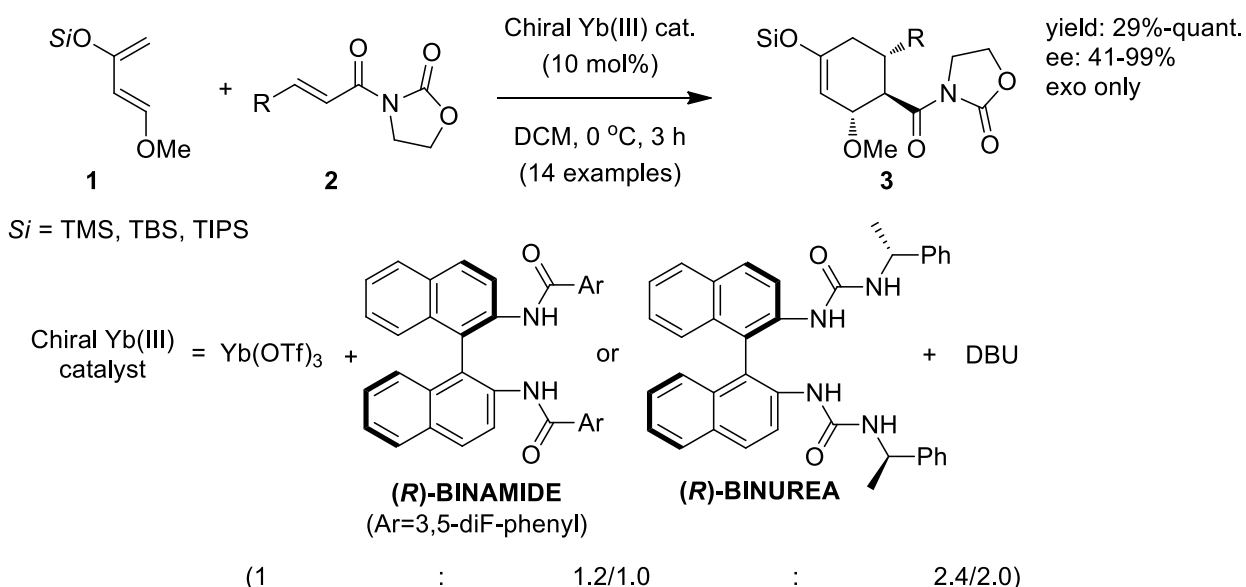
2. Cycloadditions and Cyclizations

Cycloaddition and cyclization processes, exemplified by Diels-Alder (DA), hetero-Diels-Alder (HDA) reactions and Huisgen cycloaddition, are of great importance in organic chemistry, since they provide distinct reactivity and selectivity patterns, and offer rapid entries into complex cyclic structures bearing multiple stereocenters.^{16,17} Lewis acids, including lanthanide(III) triflates, were shown to effectively catalyze cycloaddition reactions in general, allowing for lower reaction temperatures, faster times and cleaner conversions.¹⁸ Apart from possessing high oxophilicity and moisture tolerability, the uniqueness of rare-earth metal(III) triflates with regards to cycloaddition reactions consists of their ability to offer exceptionally high coordination numbers, allowing for extremely organized transition states, and consequently providing excellent stereoselectivities.^{19,20}

In this review, interesting examples of strategic utilization of rare-earth metal triflates for cycloaddition/cyclization reactions published in recent years will be highlighted, with the emphasis on advantages over conventional Lewis acids. A comprehensive treatment of all recently recorded cyclizations/cycloadditions utilizing rare-earth metal triflates is beyond the scope of this review. However, the author has attempted to provide broad coverage of diverse cyclization reaction types with the hope of reinforcing significant research activity in the area of M(III) Lewis acid catalysis. The review is organized into six main portions: carbon Diels-Alder reactions, hetero-Diels-Alder reactions, [3+2], [3+3] and [4+3] cycloadditions, hydride shift/ring closure sequences, radical cyclization processes and miscellaneous cyclization reactions.

2.1 Carbon Diels-Alder Reactions

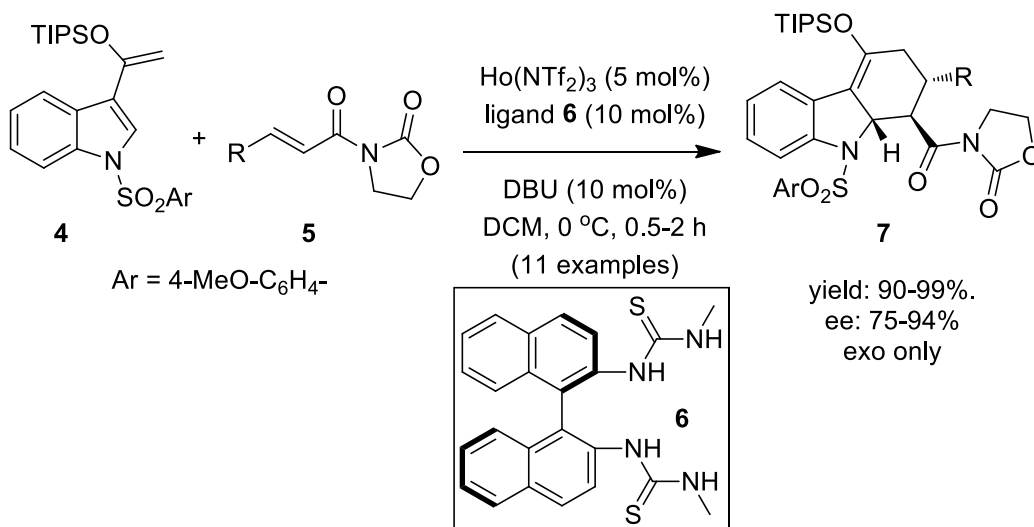
$M(OTf)_3$ have been shown to be effective catalysts for Diels-Alder reactions of various sensitive dienes and dienophiles,²¹⁻²³ and first chiral Sc(III) and Yb(III)-based catalytic systems for DA reactions were disclosed by Kobayashi and co-workers in the 1990s.^{24,25} One interesting example of asymmetric DA reaction involving Danishefsky-type dienes **1** was reported by Nishida's group.^{26,27} Specifically, complexes of $Yb(OTf)_3$, axially chiral ligands BINAMIDE and BINUREA and an amine catalyzed the DA reaction in a highly diastereo- and enantio-selective manner to provide densely functionalized chiral cyclohexenes **3**. Notably, utilization of a lanthanide triflate was the key in promoting the desired reaction without any appreciable decomposition of either substrate **2** or the reaction product **3**. The reaction is quite general, and can tolerate a variety of substituents on dienophile **2**, including aryl, alkenyl, halogens and ester moieties. The yield/enantioselectivity was lower in the case of sterically hindered dienophiles **2** bearing bulky groups (Scheme 1).



Scheme 1. Asymmetric Diels-Alder reaction catalyzed by Yb(III) complexes.

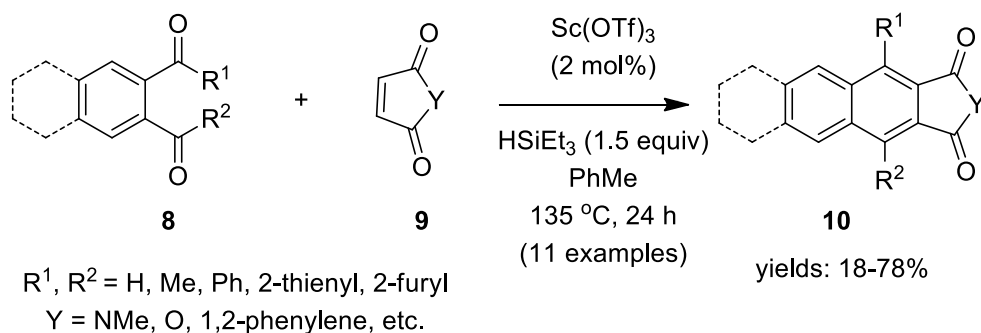
This operationally convenient and robust protocol was subsequently employed as a key step in the asymmetric total synthesis of (+)- and (-)-platyphyllide.²⁸ As a result, the absolute configuration of the natural (-)-form was revised to be the (6*S*,7*S*)-enantiomer.

A similar bis-thiourea **6**-based asymmetric catalytic system disclosed by the same research group three year later in 2013 utilizes holmium(III) Lewis acid instead of the ytterbium(III) protocol described above. The reported [4+2]-cycloaddition of silyloxyvinylindoles **4** provides an expedient stereoselective entry into hydrocarbazoles **7** (Scheme 2), as well as hydroindoles and hydrobenzofurans.²⁹ The obtained chiral cycloadducts could serve as potential synthetic intermediates for *Strychnos* alkaloids.



Scheme 2. Diels-Alder reaction of 3-siloxyvinylindole **4**.

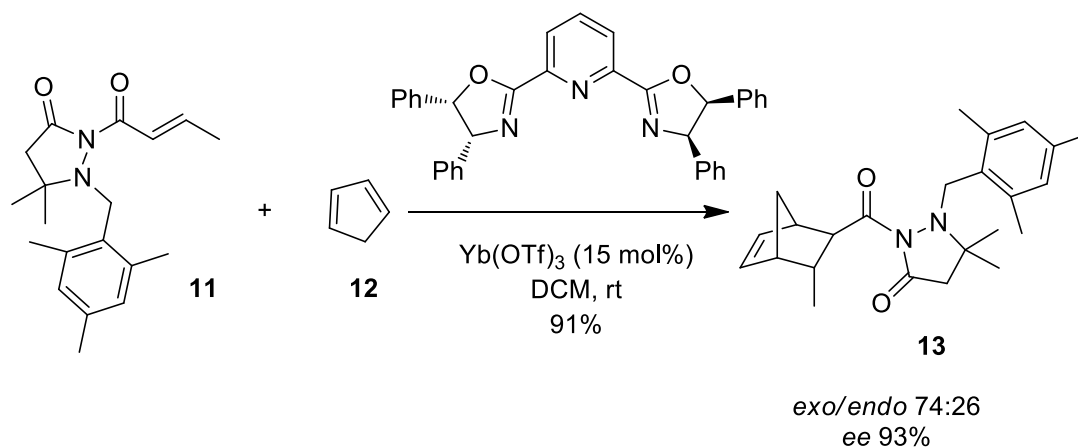
It has been demonstrated that Sc(OTf)₃ can catalyze generation and successive aromatization of isobenzofuran from *o*-dicarbonylbenzenes **8** to yield the corresponding naphthalene derivatives **10** (Scheme 3).³⁰ Sc(OTf)₃ catalyzed both hydrosilylation and



Scheme 3. Preparation of naphthalene derivatives **10**.

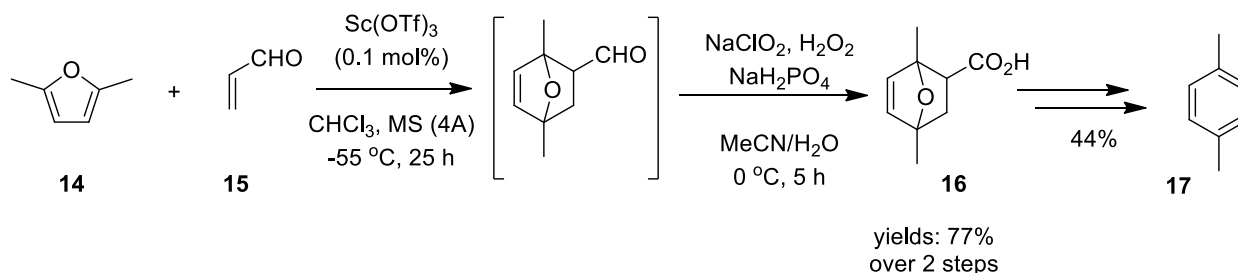
dehydration of an intermediate Diels-Alder adduct, and Sc/Amberlyst-15 recyclable catalyst was shown to be efficient for the reaction. The nature of R¹ and R² groups affected the yield of the reaction. In correlation with the hydrosilylation propensity, acetyl derivatives were less reactive, while formyl and aroyl/heteroaroyl groups provided good conversions.

Enantioselective Yb(OTf)₃/Pybox-catalyzed Diels-Alder reactions with enhanced *exo* selectivity were studied by Sibi and co-workers.³¹ The nature of a pyrazolidinone auxiliary and a Pybox ligand greatly affected the yield of *exo*-adduct **13** (Scheme 4). It is noteworthy that the Sc(OTf)₃-catalyzed reaction, as opposed to employing Yb(OTf)₃ or Y(OTf)₃, led to *endo*-selective cycloadditions.



Scheme 4. *Exo*-selective Diels-Alder reaction.

An interesting Sc(OTf)₃-mediated Diels-Alder reaction between biomass-derived 2,5-dimethylfuran **14** and acrolein **15** to produce *p*-xylene **17** was reported by Toste *et al.* in 2011 (Scheme 5).³² The described route, although not being immediately practical, demonstrated the possibility of realizing a completely bio-renewable approach to PET precursor *p*-xylene utilizing Sc(III) Lewis acid.



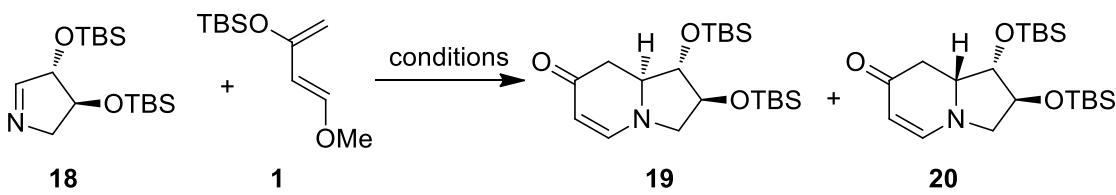
Scheme 5. Bio-renewable approach to *p*-xylene **17** using Sc(OTf)₃.

2.2 Hetero-Diels-Alder reactions

The hetero-Diels-Alder reaction has attracted significant attention over the past decades as a unique method for the assembly of complex heterocycles in a convergent and regioselective fashion, generally from simple, readily available building blocks.^{33,34} Among various synthetic methodologies available, asymmetric hetero-Diels-Alder has emerged as one of the most powerful tools for the construction of complex six-membered heterocyclic systems found in the plethora of natural products and active pharmaceutical ingredients.^{35,36} As was the case for DA reactions, rare-earth metal(III) triflates have also been successfully employed to promote hetero-Diels-Alder reactions.¹⁰⁻¹⁵ Below are notable examples of M(OTf)₃-catalyzed HDA reactions published in the last five years.

In an effort to access polyhydroxylated indolizine scaffolds, Yang and co-workers studied asymmetric aza-Diels-Alder reaction of pyrrolidine imine **18** with an excess of Danishefsky's diene **1** under various reaction conditions (Table 1).³⁷ Conventional Lewis acids like BF₃·Et₂O, ZnCl₂ and AlCl₃, gave disappointing results, expressed in either unsatisfactory diastereomeric ratios or poor yields. Gratifyingly, Yb(OTf)₃ catalyzed the reaction with excellent yields and diastereoselectivity (Table 1, entries 7, 8). This Yb(III)-mediated methodology allowed rapid and highly selective entry into stereochemically rich indolizine enaminones, and was successfully utilized in a concise syntheses of (+)-/(-)-lentiginosines and (-)-2-*epi*-stevamine.³⁷

Table 1. Lewis acid catalysis of asymmetric aza-Diels-Alder reaction^a



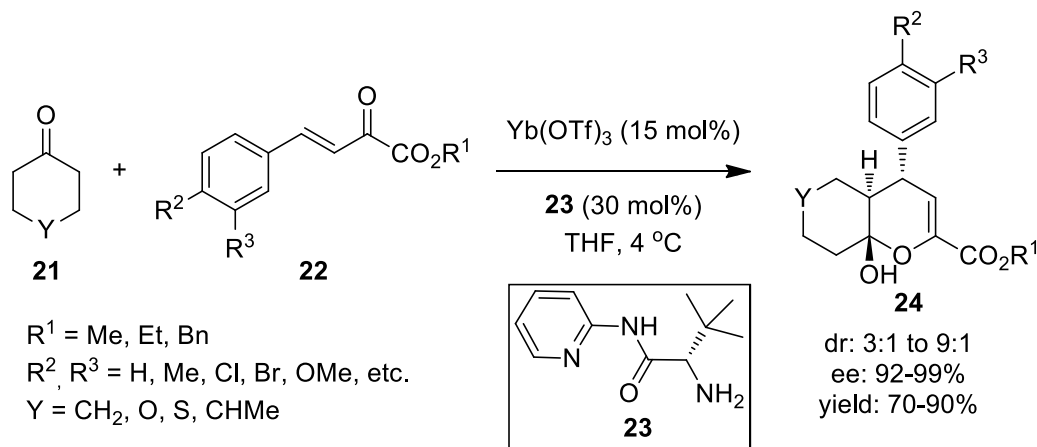
Entry	Catalyst (equiv.)	T (°C)/solvent	Yield	dr ^b
1	ZnCl ₂ (1.0)	-40 to rt / THF	36	1.9 / 1
2	ZnCl ₂ (1.0)	-40 to rt / PhMe	43	1.2 / 1
3	ZnCl ₂ (1.0)	-40 to rt / DCM	65	4 / 1
4	AlCl ₃ (1.0)	-40 / DCM	70	4.9 / 1
5	BF ₃ ·EtO ₂ (1.0)	-40 / DCM	<15	n.d.
6	AgOTf (1.0)	-40 to rt / DCM	<15	n.d.

Table 1. Continue

Entry	Catalyst (equiv.)	T (°C)/solvent	Yield	dr ^b
7	Yb(OTf) ₃ (1.0)	-40 / DCM	73	11 / 1
8	Yb(OTf) ₃ (0.5)	-40 to 0 / DCM	73	11 / 1

^a Preformed with **18** (1.0 equiv), **1** (1.0 equiv), and catalyst in anhydrous solvent for 3 h. ^b Ratio **19/20**, determined by ¹H-NMR.

Lanthanide triflates were employed by Wang and his group in the context of novel organocatalyst/metal Lewis acid bifunctional catalytic system to tackle a long-standing challenge of asymmetric inverse electron-demand hetero-Diels-Alder (IED/HDA) of cyclic ketones (Scheme 6).³⁸ During the initial metal salt co-catalyst screen, Cu(SbF₆)₂, Sc(OTf)₃ and Eu(fod)₃ yielded exclusively an aldol side-product. On the other hand, La(OTf)₃, Y(OTf)₃ and Yb(OTf)₃ produced the desired product **24**; the latter catalyst Yb(OTf)₃ was selected because of superior chemo-, diastereo- and enantioselectivity (Scheme 6). In terms of substrate scope, a wide range of ketones **21** and enones **22** reacted smoothly providing bicycles **24** with excellent diastereo- and enantioselectivities and in high yields. Remarkably, no aldol side-product was detected for the majority of the reactions, except for heterocyclic ketones **21** (Y = O, S) and γ -3-nitrophenyl enone **22**.

**Scheme 6.** Asymmetric IED/HDA with Yb(OTf)₃ and primary amine ligand **23**.

It is worth mentioning that only two *endo* diastereomers were observed during this hetero-Diels-Alder reaction, despite the fact that three to four stereogenic centers were formed. The sense of asymmetric induction could be rationalized by assuming the formation of octahedral

Yb(III)-diene complex **25** (Figure 1). The bulky *tert*-butyl group from the amine ligand **23** effectively shields the *Re* face of the enamine, and enone approaches from the *Si* face, to afford the product with the observed absolute configuration.³⁸

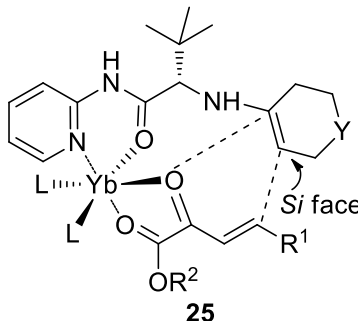
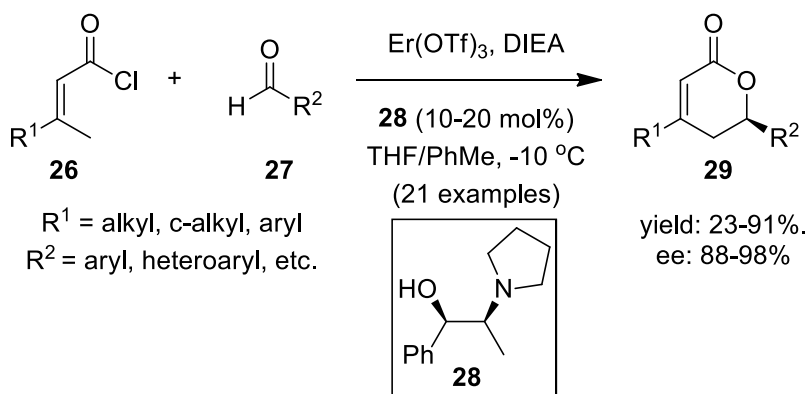


Figure 1. Proposed transition state.

An unprecedented Er(OTf)₃-mediated hetero-Diels-Alder reaction of α,β -unsaturated acid chlorides **26** with aromatic and heteroaromatic aldehydes **27** to give synthetically useful δ -lactones **29** was developed by Peters and co-workers.³⁹ Er(OTf)₃ was selected due to its considerably lower cost compared to other lanthanide triflates, and relatively small ionic radius favoring highly organized transition states. The generality of this cooperative bifunctional Lewis acid-Lewis base catalytic approach was demonstrated on a variety of substrates bearing methoxy-, trifluoromethyl-, halo-, and nitroaryl, as well as heteroaryl moieties (Scheme 7). It should be noted that electron-donating groups on aryl aldehydes **27** resulted in lower yields, while electron-withdrawing groups enhanced the reactivity.

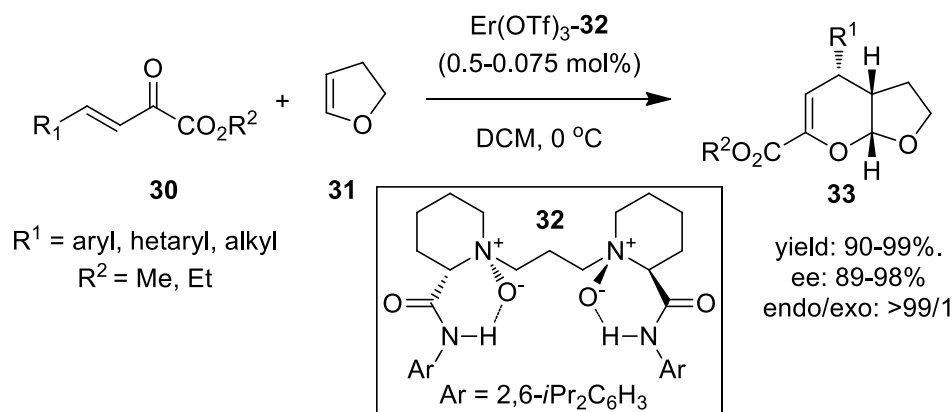


Scheme 7. HDA reaction leading to δ -lactones **29**.

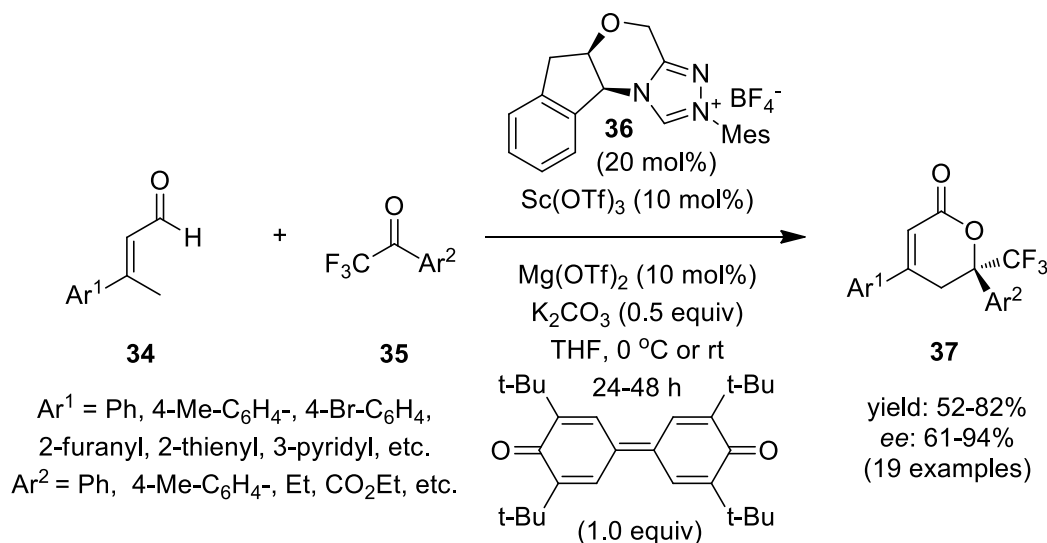
Another application of Er(OTf)₃ for a highly enantioselective synthesis of 3,4-dihydro-2*H*-pyrans **33** featuring remarkably low catalyst loading (0.5-0.075 mol%) was reported by Feng and co-workers in 2011.⁴⁰ This protocol utilizes the highly efficient N,N'-dioxide ligand **32**, which putatively forms the [(**32**)₂Er(OTf)₃] complex as suggested by a positive non-linear effect. Initial

metal salts screen revealed that traditional Lewis acids like Fe(III) and Cu(II) gave poor results, while Ln(III) triflates—Er(OTf)₃ being the most efficient—provided favorable conversion and enantioselectivity. A broad range of functional groups on β,γ -unsaturated α -ketoesters **30** is tolerated. The reaction proceeds in DCM at 0 °C, providing target products **33** in excellent chemical yields, as well as enantio- and diastereomeric excess, and could be scaled up to gram quantities with the same outstanding results (Scheme 8).

As was mentioned above, M(III)-based Lewis acids have exceptional affinities to carbonyl oxygens and carboxylates, thus allowing for extremely organized transition states for substrates bearing these moieties. This fact was utilized by Chi *et al.* in the course of developing highly enantioselective condensation of enals **34** with trifluoroketones **35** under N-heterocyclic carbene (NHC) catalysis (Scheme 9).⁴¹ The usage of Sc(OTf)₃ as a Lewis acid co-catalyst resulted in a remarkable amplification of an otherwise weak chiral induction by enantiopure NHC **36**.

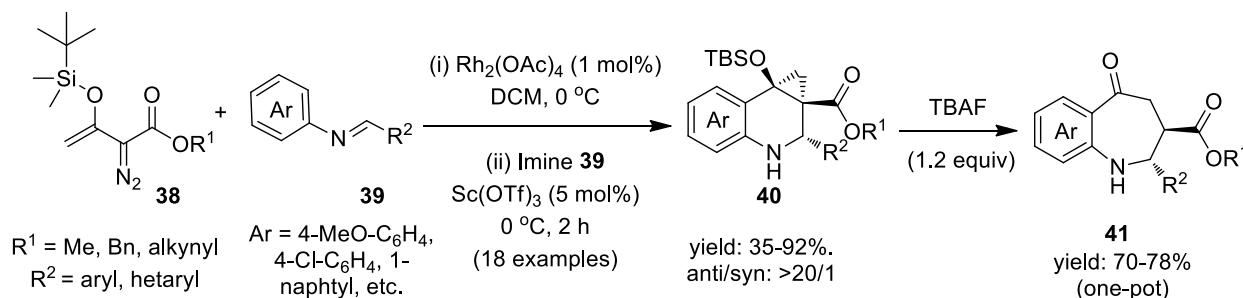


Scheme 8. Enantioselective HDA reaction of DHF **31** and β,γ -unsaturated α -ketoesters **30**.



Scheme 9. Sc(OTf)₃-NHC cooperative catalysis.

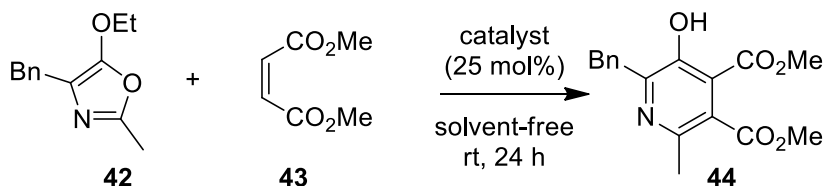
In another report, Doyle and his group disclosed a $\text{Sc}(\text{OTf})_3$ -catalyzed method for the preparation of tetrahydroquinolines and benzazepines via a Povarov reaction.^{42,43} Upon treatment with $\text{Rh}_2(\text{OAc})_4$, enoldiazoacetates **38** undergo dinitrogen extrusion, and the generated donor-acceptor cyclopropenes react with imine counterparts **39** to afford target tetrahydroquinolines **40** in a highly regio- and stereoselective fashion (Scheme 10).⁴⁴ Surveying a variety of Lewis and Brønsted acid catalysts identified $\text{Sc}(\text{OTf})_3$ as the catalyst of choice for this transformation. The reaction is quite general and provides excellent yields of Povarov products for both electron-donating and moderately electron-accepting groups on imine **39**, as well as heteroaryl imines. However, in the case of a strongly electron-withdrawing nitro group the transformation proceeded with diminished efficiency. The obtained fused cyclopropane tetrahydroquinolines **40** upon treatment with TBAF could be further elaborated into 1*H*-benzazepine privileged structures **41** (Scheme 10).



Scheme 10. $\text{Sc}(\text{OTf})_3$ -promoted Povarov reaction and benzazepines synthesis.

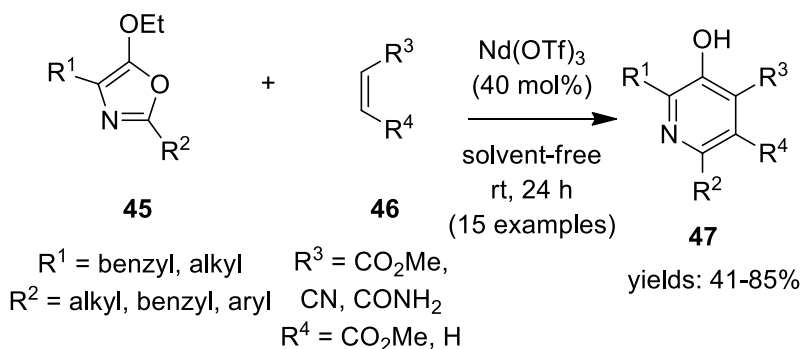
A general, single-step, solventless procedure to access medicinally important 3-hydroxy-pyridine scaffold **47** via Kondrat'eva hetero-Diels-Alder reaction⁴⁵ was reported by Renard *et al.*⁴⁶ While $\text{Hf}(\text{IV})$ and $\text{Cu}(\text{II})$ triflates were unsuccessfully explored for the transformation, $\text{La}(\text{III})$, $\text{Sm}(\text{III})$ and $\text{Nd}(\text{III})$ notably improved the reaction efficiency (Table 2).

The scope of the aforementioned $\text{Nd}(\text{III})$ -catalyzed reaction is rather broad, and a wide range of substituents were tolerated on both oxazoles **45** and dienophile **46** components (Scheme 11). It should be noted that small substituents at position 5 of the oxazole **45** afforded target pyridines **47** in lower yield, presumably due to partial hydrolysis of the unstable intermediate cycloadduct. The reaction was applied towards highly functionalized furopyridine derivatives possessing MEK kinase inhibitory activity.⁴⁶

Table 2. Survey of Lewis acids for the synthesis of 3-hydroxypyridines

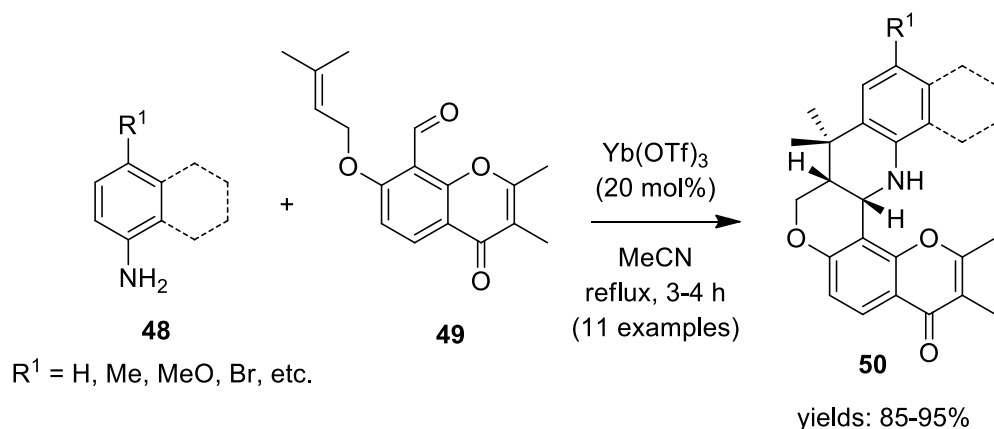
Entry	Catalyst	Yield ^a
1	None	0
2	Sc(OTf) ₃	10
3	Eu(OTf) ₃	31
4	Yb(OTf) ₃	38
5	La(OTf) ₃	57
6	Sm(OTf) ₃	58
7	Nd(OTf) ₃	59 (72) ^b
8	TfOH	0
9	Hf(OTf) ₄ ·H ₂ O	<5
10	Cu(OTf) ₂	0

^a Yield determined by ¹H-NMR of the crude reaction mixture relative to **42**. ^b Isolated yield using 40 mol% of Nd(OTf)₃.

**Scheme 11.** Scope of Nd(III)-catalyzed Kondrat'eva reaction.

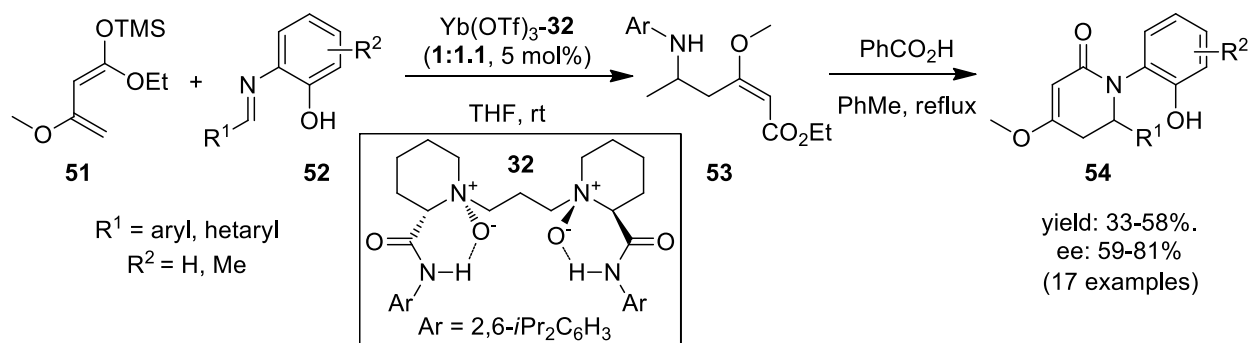
A mild and efficient approach to *cis*-fused tetrahydrochromeno[4,3-*b*]quinolines via intramolecular Povarov reaction of aromatic amines **48** with 7-*O*-prenyl-8-formyl chromenones **49** was reported.⁴⁷ Among the catalysts surveyed (ZnCl₂, NbCl₅, FeCl₃, etc.), the best results in terms of reaction times, yields, and diastereoselectivity were obtained with Yb(OTf)₃ in refluxing MeCN (Scheme 12). A number of new *cis*-fused tetrahydrochromeno[4,3-*b*]quinolines **50**

demonstrated significant antiproliferative effects in breast cancer cell lines comparable to Tamoxifen.



Scheme 12. Yb(III)-catalyzed synthesis of tetrahydrochromeno[4,3-*b*]quinolines analogs.

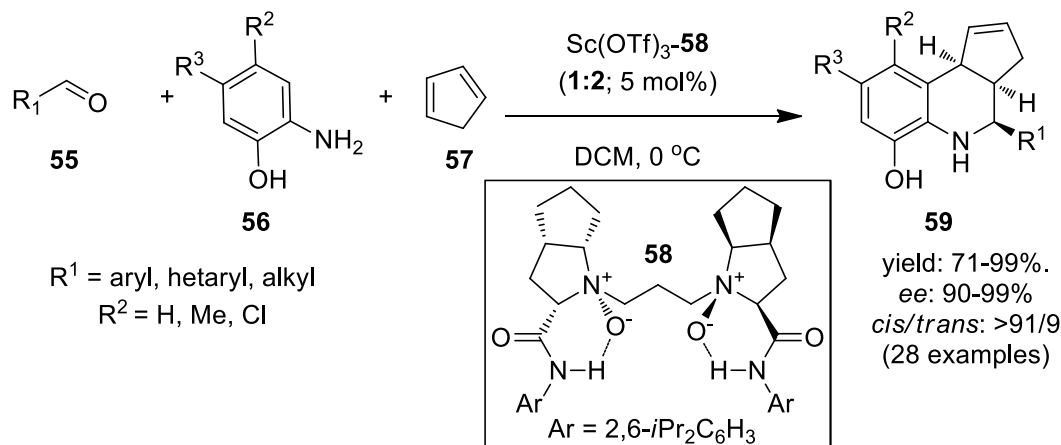
A catalytic enantioselective aza-Diels-Alder reaction of Brassard's diene **51** with aldimines **52** was reported.⁴⁸ In contrast with Danishefsky's diene, a double substitution in Brassard's diene terminus hindered the enantioselectivity of the hetero-Diels-Alder reaction under standard conditions. Gratifyingly, a complex of previously mentioned *N,N'*-dioxide **32** with Yb(OTf)₃ afforded the corresponding α,β -unsaturated γ -lactone derivatives **54** in a two-step process via a Mannich product **53** with moderate to good yields and good enantioselectivities (Scheme 13).



Scheme 13. Enantioselective Yb(III)-catalyzed aza-Diels-Alder reaction with Brassard's diene.

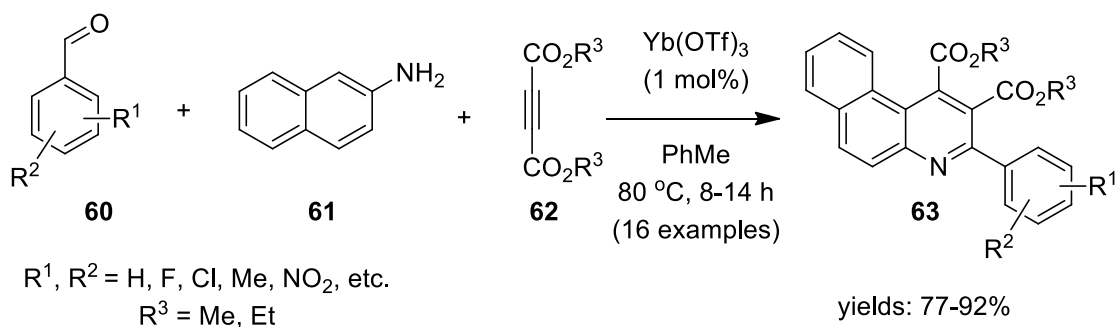
A structurally related *L*-ramipril-acid-derived *N,N'*-dioxide **58** ligand was successfully employed in a Sc(OTf)₃-catalyzed three-component inverse electron-demand aza-Diels-Alder reaction (IEDDA) to yield ring-fused tetrahydroquinolines **59** with high enantio- and diastereoselectivities.⁴⁹ Feng *et al.* demonstrated that Sc(OTf)₃ was a superior co-catalyst for the reaction, and the reaction tolerated a wide range of electronically and sterically diverse aldehydes **55** (Scheme 14). The reaction was successfully performed on gram scale without any loss of

selectivity, and the obtained material was structurally elaborated further to tetrahydroquinoline derivatives of potential medicinal importance.



Scheme 14. Asymmetric $\text{Sc}(\text{OTf})_3$ -catalyzed IEDDA reaction.

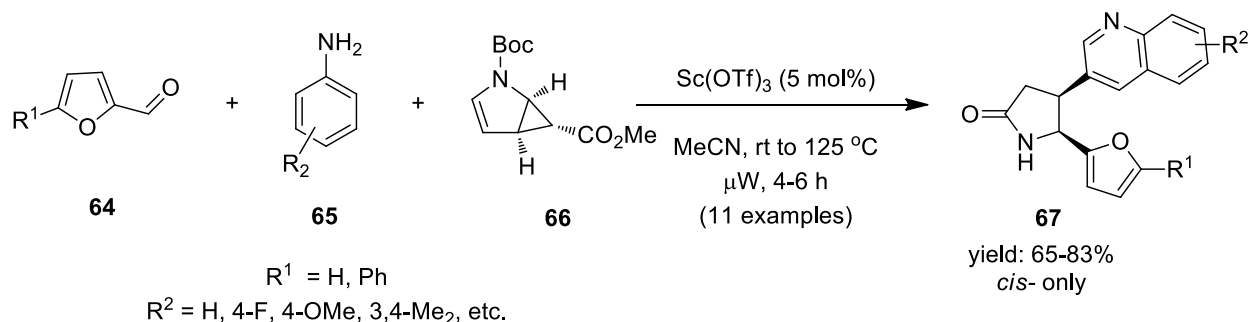
The fact that $\text{Yb}(\text{OTf})_3$ efficiently activates Schiff bases for the hetero-Diels-Alder reaction has motivated Wang *et al.* to study a three-component reaction of aromatic aldehydes **60**, naphthalen-2-amine **61**, and but-2-ynedioate **62** to yield 3-arylbenzo[*f*]quinoline-1,2-dicarboxylates **63**.⁵⁰ Indeed, a broad range of aromatic aldehydes, bearing both electron-accepting and electron-donating groups, reacted smoothly to produce the desired products (Scheme 15).



Scheme 15. $\text{Sc}(\text{OTf})_3$ -catalyzed three-component reaction.

Cis-4,5-substituted pyrrolidinones bearing aromatic and heteroaromatic groups are considered structures of medicinal importance.⁵¹ A novel, operationally simple, three-component assembly of these privileged structures, based on readily available furancarbaldehydes **64**, anilines **65**, and cyclopropanated N-Boc pyrrole **66**, was reported in 2012 (Scheme 16).⁵² Among a number of Lewis acids screened, $\text{Sc}(\text{OTf})_3$ was found to be the optimal catalyst for the transformation. A plausible mechanism of this reaction, involving $\text{Sc}(\text{OTf})_3$ -mediated

cyclopropane ring opening, furan migration, and final rearomatization leading to a range of functionalized *cis*-pyrrolidinones **67**, was proposed.⁵¹

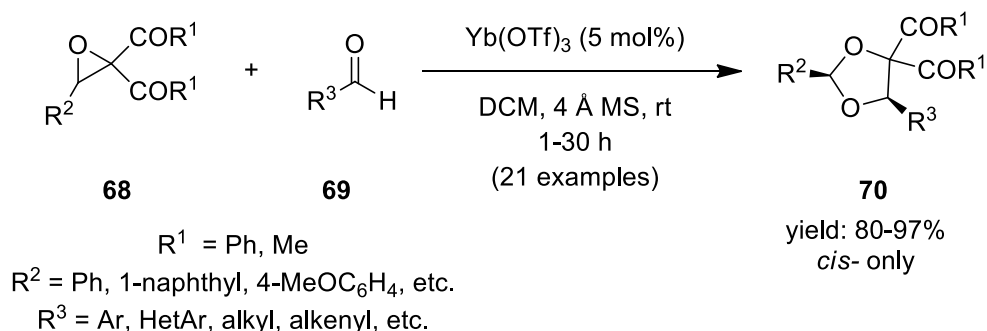


Scheme 16. Three-component assembly of *cis*-4,5-substituted pyrrolidinones **67**.

2.3 [3+2] Cycloadditions and related processes

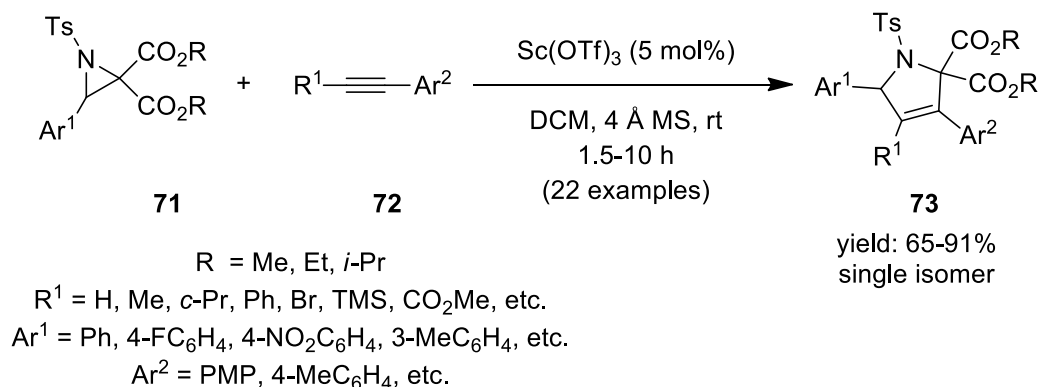
1,3-Dipolar cycloaddition is one of the most important reaction classes in synthetic heterocyclic chemistry, and it has found broad application as an efficient, regio- and stereocontrolled, and high-yielding method for the synthesis of diverse heterocyclic systems of considerable complexity.^{17,53-55} Discussed below is a selection of compelling examples of $\text{M}(\text{OTf})_3$ -catalyzed [3+2] cycloadditions and related processes published in the last five years.

The generation of reactive carbonyl ylides via mild $\text{Yb}(\text{OTf})_3$ -catalyzed C-C heterolysis of the respective oxiranes **68** was disclosed by Zhang *et al.*⁵⁶ Among Lewis acids tested to effect the transformation, conventional Lewis acids such as $\text{Sn}(\text{OTf})_2$, $\text{Bi}(\text{OTf})_3$, $\text{Fe}(\text{OTf})_3$, and $\text{Mg}(\text{OTf})_2$ resulted in either low efficiency or no catalytic activity. On the other hand, $\text{Sc}(\text{OTf})_3$, $\text{Y}(\text{OTf})_3$ and $\text{Yb}(\text{OTf})_3$ effected smooth reaction. The latter catalyst was marginally better for carbonyl ylide generation, and subsequent [3+2] cycloaddition of the generated carbonyl ylides with a range of aldehydes afforded synthetically useful *cis*-1,3-disubstituted 1,3-dioxolanes **70** in excellent yields (Scheme 17). A mechanism for the aforementioned transformation, featuring direct oxiranes **68** C-C bond heterolysis, followed by a reaction of Yb-coordinated ylide with aldehydes **69** and final ring closure, was postulated.



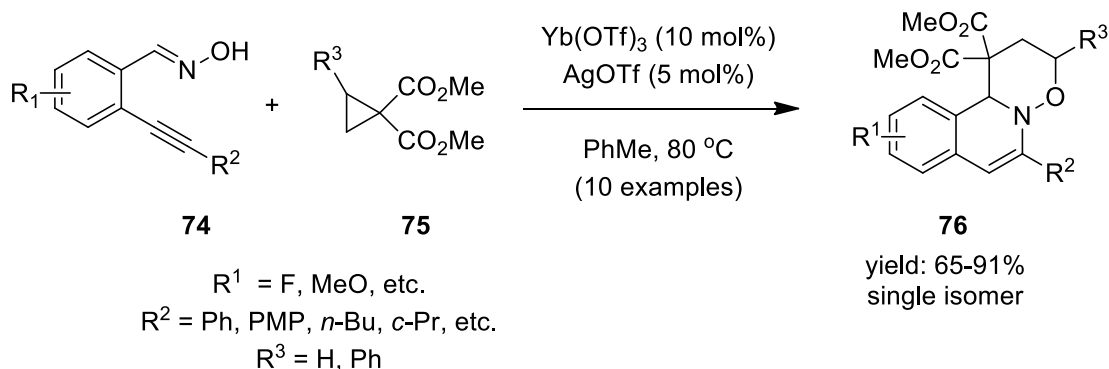
Scheme 17. 1,3-Dipolar cycloaddition catalyzed by $\text{Yb}(\text{OTf})_3$.

In a subsequent publication, the same research group disclosed a highly regioselective Sc(OTf)₃-catalyzed 1,3-dipolar cycloaddition of alkynes with azomethine ylides providing highly substituted 3-pyrrolines **73** (Scheme 18).⁵⁷ Analogous to a previous transformation, Ln(OTf)₃ was a key reagent to effect facile generation of azomethine ylides from N-Tos aziridines **71** via C-C heterolysis. Preliminary investigations revealed that moderate enantioselectivity can be achieved with a PyBox ligand.



Scheme 18. Preparation of 3-pyrrolines **73** via [3+2] cycloaddition.

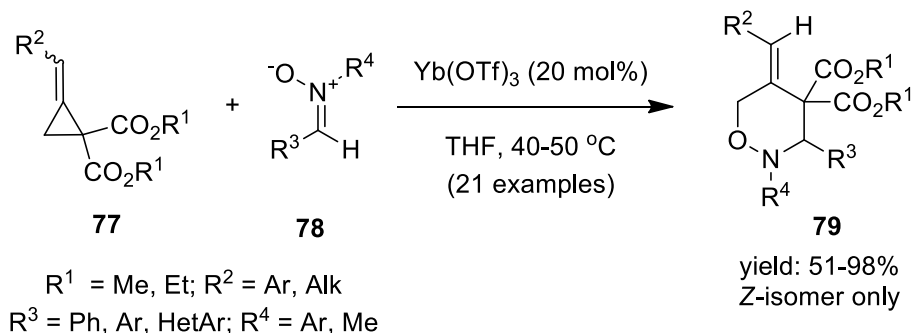
An interesting tandem cyclization/[3+3] cycloaddition of 2-alkynylbenzaldoximes **74** with dimethyl cyclopropane-1,1-carboxylates **75**, co-catalyzed by AgOTf and Yb(OTf)₃, was reported by Wu and co-workers (Scheme 19).⁵⁸ This dually-catalyzed procedure represents a facile and useful protocol to prepare tetrahydro-1,2-oxazine fused 1,2-dihydroisoquinolines **76**, which may serve as building blocks for pharmaceutically active compounds.



Scheme 19. Tandem cyclization/[3+3] cycloaddition.

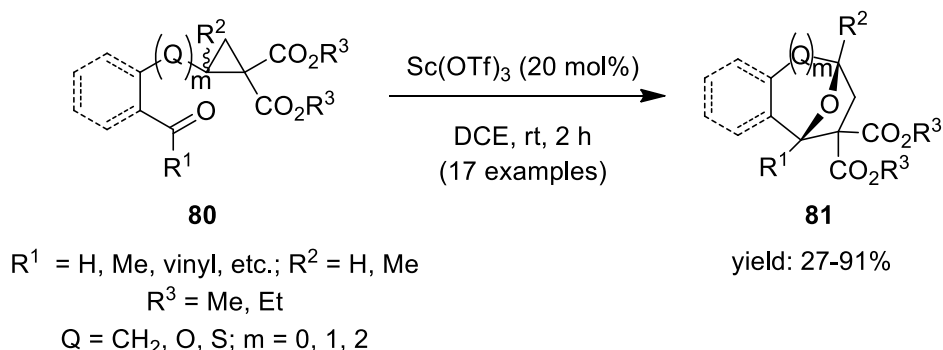
A variety of structurally diverse tetrahydro-1,2-oxazines **79** can be prepared by treatment of methylenecyclopropane-1,1-diester (MCP) **77** with C,N-disubstituted nitrones **78** in the presence of Yb(OTf)₃ (Scheme 20).⁵⁹ Sc(OTf)₃ and Mg(ClO₄)₂·6H₂O also promoted the reaction,

albeit with lower efficiency. While aryl-substituted nitrones **78** converted to tetrahydro-1,2-oxazines **79** smoothly, it should be mentioned that reactions of C,N-dialkyl nitrones did not give positive results, presumably due to the intrinsic instability of such nitrones to Lewis acids. A three-component, one-pot adaptation of this distal [3+3] cycloaddition, consisting of *in situ* generation of C,N-diarylnitrone reagents, was also developed.



Scheme 20. Synthesis of 1,2-oxazines **79**.

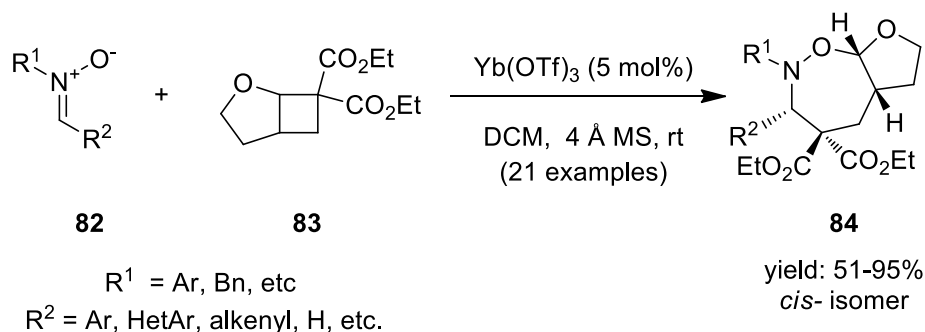
Wang *et al.* developed an intramolecular [3+2] cross-cycloaddition of donor-acceptor cyclopropanes with aldehydes or ketones for the construction of bridged oxa-[n.2.1.] skeletons **81** (Scheme 21).⁶⁰ The reaction is promoted by Sc(OTf)_3 , proceeds in a stereoselective manner and can also be applied successfully towards imines to yield aza-[n.2.1.] systems. The reported methodology was showcased in the course of a platensimycin formal synthesis and a (\pm)-bruguierol A total synthesis.^{61,62} The same Sc(OTf)_3 methodology subsequently was utilized to expediently construct bridged [n.2.1] carbocyclic systems via a novel intramolecular [3+2] process involving alkenes and donor-acceptor cyclopropanes.⁶³ The strategy was successfully applied to the total synthesis of tetracyclic diterpenoids phyllocladanol and phyllocladene.



Scheme 21. Construction of oxa-[n.2.1] skeletons **81**.

A logical extension of the analogous M(OTf)_3 -catalyzed cycloaddition reactions to homologous donor-acceptor cyclobutanes was reported in 2009-2011 by Johnson⁶⁴ and

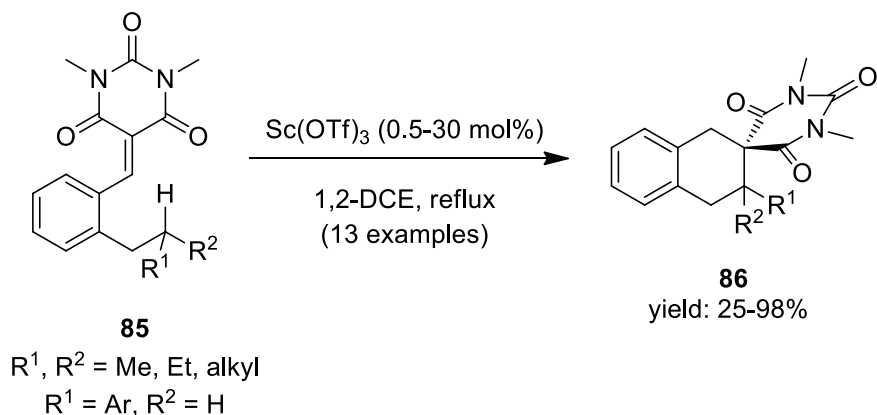
Pagenkopf.^{65,66} For instance, structurally unique 2,3,4,6,7-substituted oxazepines **84** can be prepared from a wide selection of nitrones **82** and activated donor-acceptor cyclobutane **83** (Scheme 22).⁶⁷ This formal [4+3] cycloaddition is catalyzed by $\text{Yb}(\text{OTf})_3$, and, in most cases, initially affords a diastereomeric mixture, which equilibrates to a single diastereomer. Nitrones **82** bearing both electron-rich and electron-deficient N-aryl groups were found to be viable cycloaddition partners.



Scheme 22. Formal [4+3] cycloaddition of donor-acceptor cyclobutane **83**.

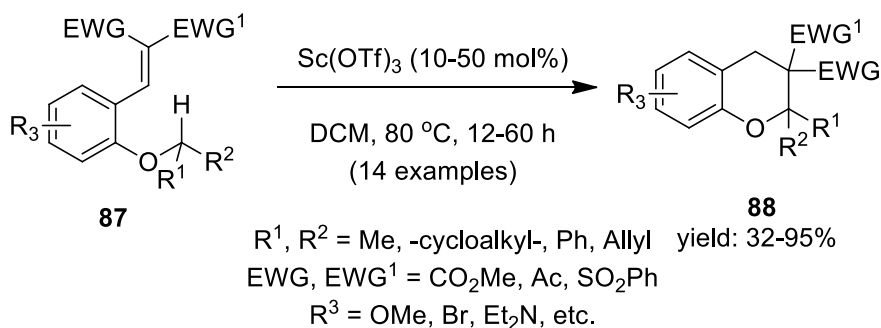
2.4 [1,5]-H Shift/ring closure reactions

In the last decade $\text{sp}^3\text{-C-H}$ bond functionalization via an internal redox process, which involves a [1,5]-hydride shift from the activated carbon atom, followed by cyclization, has attracted much attention. Specifically, $\text{Sc}(\text{OTf})_3$ was used to achieve [1,5]-H shift mediated C-H bond functionalization to furnish tetraline derivatives **86** (Scheme 23).^{68,69} It should be noted that sterically hindered substrates **85** (*e.g.* $\text{R}^1 = \text{Mes}$) showed considerably lower reactivity, and required higher $\text{Sc}(\text{OTf})_3$ catalyst loadings. Remarkably, the reaction is operational for purely aliphatic substrates **85**, and γ -alkyl side chain substrates provided unexpected indane derivatives via [1,6]-H process.⁶⁸



Scheme 23. $\text{Sc}(\text{OTf})_3$ -catalyzed hydride shift/cyclization.

An analogous $\text{Sc}(\text{OTf})_3$ -mediated hydride-transfer cyclization of *ortho*-vinylaryl alkyl ethers **87** was reported by Sames and co-workers (Scheme 24).⁷⁰ Other Lewis acids including $\text{BF}_3 \cdot \text{Et}_2\text{O}$, PtCl_4 , TiCl_4 , and $\text{Cu}(\text{OTf})_2$ were much less efficient, resulting in no conversion or low reaction rates. It should be noted that other members of the lanthanide family, $\text{Yb}(\text{OTf})_3$ and $\text{Gd}(\text{OTf})_3$, were less efficient catalysts as well, underscoring the unique catalytic activity of scandium triflate for this transformation.



Scheme 24. Preparation of dihydrobenzopyrans **88**.

In an effort to develop intramolecular redox C-H functionalization to access tetrahydroquinolines, Seidel and his research group studied [1,5]-hydride shift/ring closure of *N*-arylamines **89** under various reaction conditions (Table 3).⁷¹ Among the Lewis acids tested, $\text{Sc}(\text{OTf})_3$ and $\text{La}(\text{OTf})_3$ served as effective reaction promoters. Further, gadolinium triflate showed remarkable rate acceleration in the series of tested catalysts (entries 13 and 16) and was ultimately selected as a catalyst of choice for the reaction.

Table 3. Screening of Lewis acid catalysts ^a

Entry	Catalyst	Mol %	Solvent	Time	Yield (%)
1	$\text{Mg}(\text{OTf})_2$	20	DCM	24 h	20 ^b
2	$\text{Mg}(\text{ClO}_4)_2$	20	DCM	20 h	83
3	$\text{Mg}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$	20	DCM	24 h	Trace
4	InCl_3	20	DCM	24 h	66 ^b
5	$\text{Zn}(\text{OTf})_2$	20	DCM	24 h	72 ^b

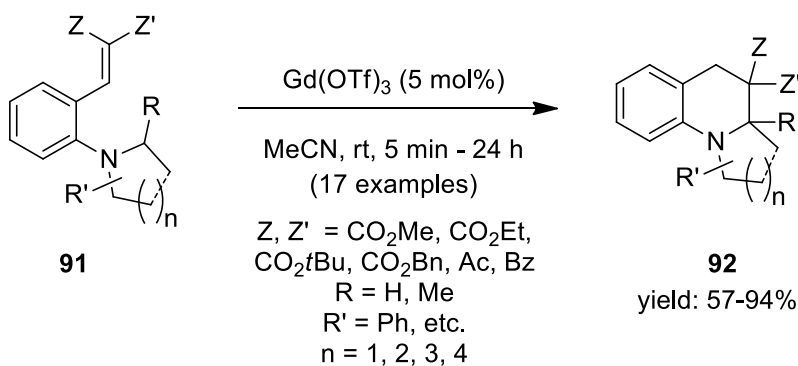
Table 3. Continued

Entry	Catalyst	Mol %	Solvent	Time	Yield (%)
6	Cu(OTf) ₂	20	DCM	24 h	55
7	Ni(ClO ₄) ₂ ·6H ₂ O	20	DCM	24 h	28 ^b
8	FeCl ₃ ·6H ₂ O	20	DCM	24 h	Trace
9	Yb(OTf) ₃	20	DCM	2.5 h	84
10	Sc(OTf) ₃	20	DCM	30 min	86
11	Sc(OTf) ₃	20	MeCN	1 h	93
12	Sc(OTf) ₃	10	MeCN	4 h	93
13	Sc(OTf) ₃	5	MeCN	22 h	83
14	La(OTf) ₃	10	MeCN	45 min	86
15	Gd(OTf) ₃	10	MeCN	15 min	93
16	Gd(OTf) ₃	5	MeCN	15 min	90
17	Gd(OTf) ₃	5	DCM	50 min	75

Performed on 0.25 mmol scale in a given solvent (0.1 M) to full conversion by TLC analysis.

^b Determined by ¹H-NMR.

The aforementioned cyclization protocol showed wide reaction scope with respect to both the amine donor moiety and the acceptor residue, allowing rapid access to complex tetrahydroquinolines **92** (Scheme 25).⁷¹ The transformation is rather general, with the exception of dinitrile derivatives **91** (Z, Z' = CN), which could be explained by the limited propensity of CN groups to engage in chelating interactions. Preliminary results indicated that the reaction could be performed in an enantioselective fashion utilizing a Box ligand.

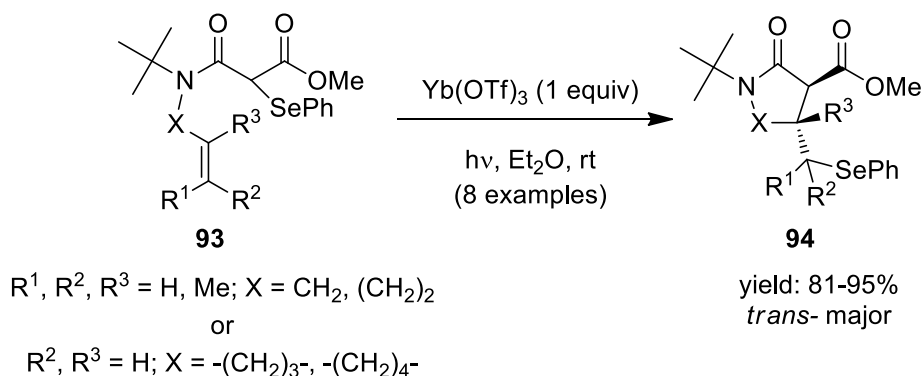
**Scheme 25.** Efficient Gd(III)-catalyzed cyclization.

2.5 Radical cyclizations

In the past 20 years, free radical reactions have received much attention, and a wide variety of synthetic methods has been developed in the field.⁷² The use of Lewis acids in radical reactions

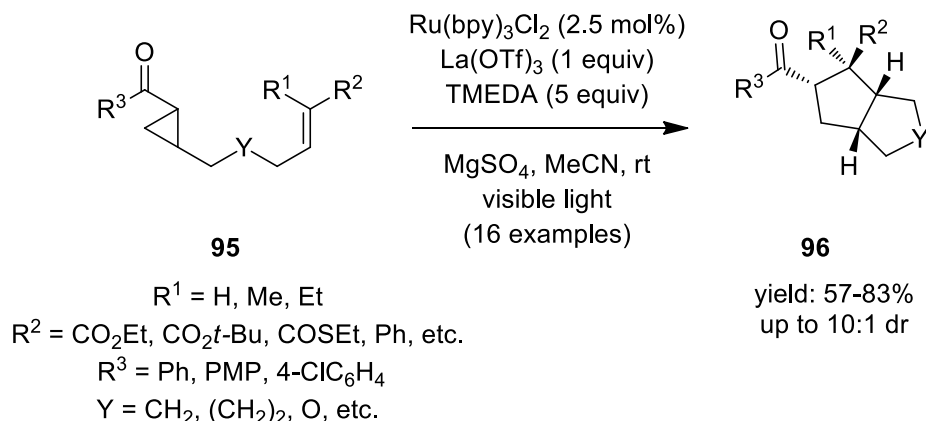
to control reactivity as well as regio- and stereoselectivity was likewise a subject of numerous research publications in the past two decades.⁷³ Owing to their oxophilic character, water tolerability and pronounced Lewis acidic properties, lanthanide triflates were also successfully employed in a number of free radical processes.¹⁰⁻¹⁵

Yang and co-workers have disclosed Yb(OTf)₃-promoted 5-/6-*exo-trig* radical cyclization of α -phenylseleno amido esters **93** under UV irradiation to give rise to mono- and bicyclic nitrogen heterocycles **94** (Scheme 26).⁷⁴ It was suggested that Yb(OTf)₃ played a two-fold role in promoting the radical process: increased electrophilicity of the α -radical intermediate via 1,3-dicarbonyl moiety chelation and accelerated PhSe group transfer.



Scheme 26. Yb(OTf)₃-promoted radical cyclization.

In 2011, Yoon *et al.* reported a photocatalytic intramolecular cyclization of alkenyl cyclopropyl ketones **95**, which is accomplished using a system comprised of La(OTf)₃, Ru(bpy)₃²⁺ and TMEDA (Scheme 27).⁷⁵ The cyclization involves generation of a distonic radical anion, which upon sequential radical cyclization, and loss of electrons produces cyclopentane-containing frameworks **96** in a rapid diastereoselective fashion. La(OTf)₃ was critical to the efficiency of the reaction and was presumably activating substrate **95** towards one-electron reduction *via* chelation.

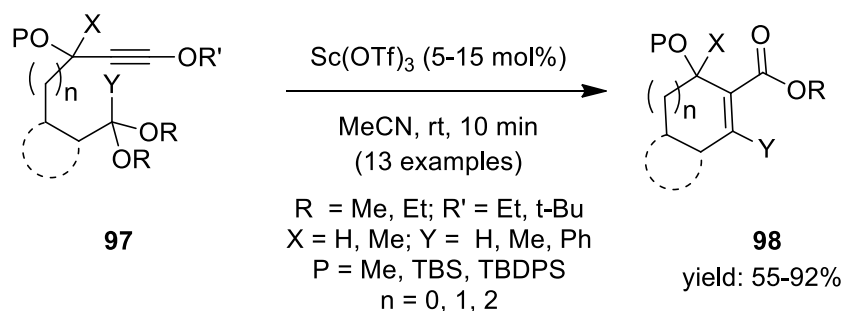


Scheme 27. Scope of photocatalytic intramolecular cyclization.

2.6 Other cyclization reactions

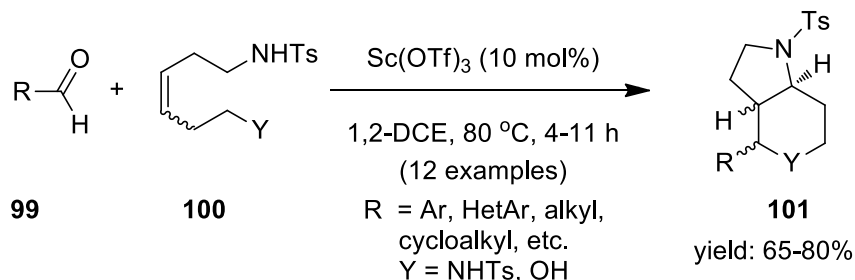
In addition to the reaction classes discussed above, rare earth metal triflates efficiently catalyze a number of other cyclization processes.¹⁰⁻¹⁵ A selection of recent examples of these useful organic transformations, including Prins-type cyclization, three-component cyclization, and heterocycle syntheses, will be highlighted in this section.

Sc(OTf)₃ can be successfully used as a promoter for intramolecular condensations of ynol ether-acetals. Specifically, Minehan and his group have disclosed a facile procedure to access 5-, 6- and 7-membered alkoxycycloalkane carboxylates **98** in good to excellent yields under mild reaction conditions (Scheme 28).⁷⁶ The obtained compounds **98** may serve as useful intermediates for natural product synthesis.



Scheme 28. Synthesis of alkoxycycloalkene carboxylates **98**.

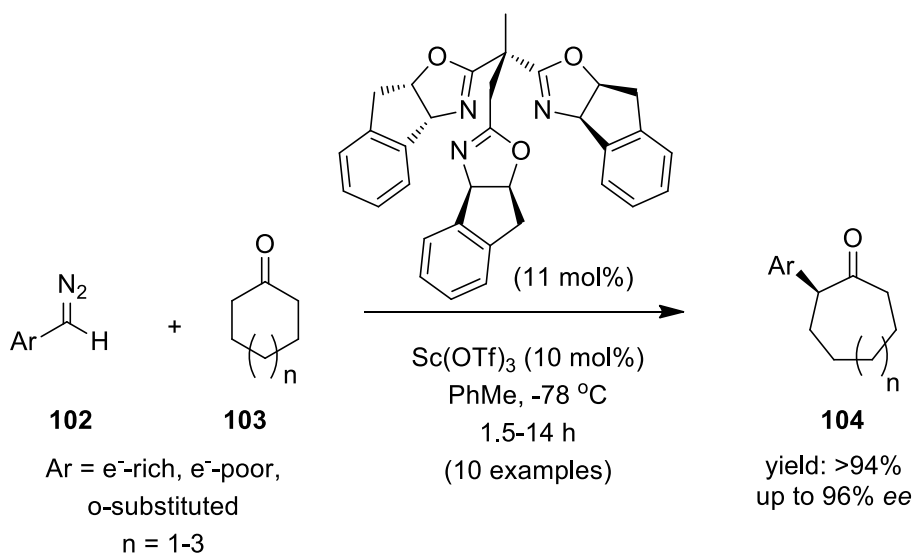
In contrast to employing strong acids and harsh reaction conditions for classical Prins cyclization, Subba Reddy and co-workers reported that the intramolecular Prins cyclization was efficiently promoted by Sc(OTf)₃ in DCE under mild heating (Scheme 29).⁷⁷ The reaction represents an entirely new approach for synthesizing heterobicycles **101** from aldehydes **99** and bis-homoallyl derivatives **100** in a convenient one-pot operation.



Scheme 29. Sc(OTf)₃-catalyzed Prins cyclization.

In a series of publications, Kingsbury and his research group disclosed robust scandium(III) triflate-catalyzed diazoalkane-carbonyl homologations to access functionalized ketones in a rapid fashion and in excellent chemical yields.⁷⁸⁻⁸¹ Sc(OTf)₃ appeared to be a highly active catalyst for

the transformation, with the catalyst loadings as low as 0.5 mol% on reaction scales up to 5 mmol.⁸¹ It deserves mentioning that during the initial attempt to identify suitable catalysts for the transformation, various aluminum- and boron-based Lewis acids were screened unsuccessfully.⁷⁸ The enantioselective version of this protocol was reported, allowing access to medium ring 2-aryl cyclic ketones **104** from the respective cyclic ketones **103** in one step in virtually quantitative yields and in up to 96% *ee* (Scheme 30).⁸⁰

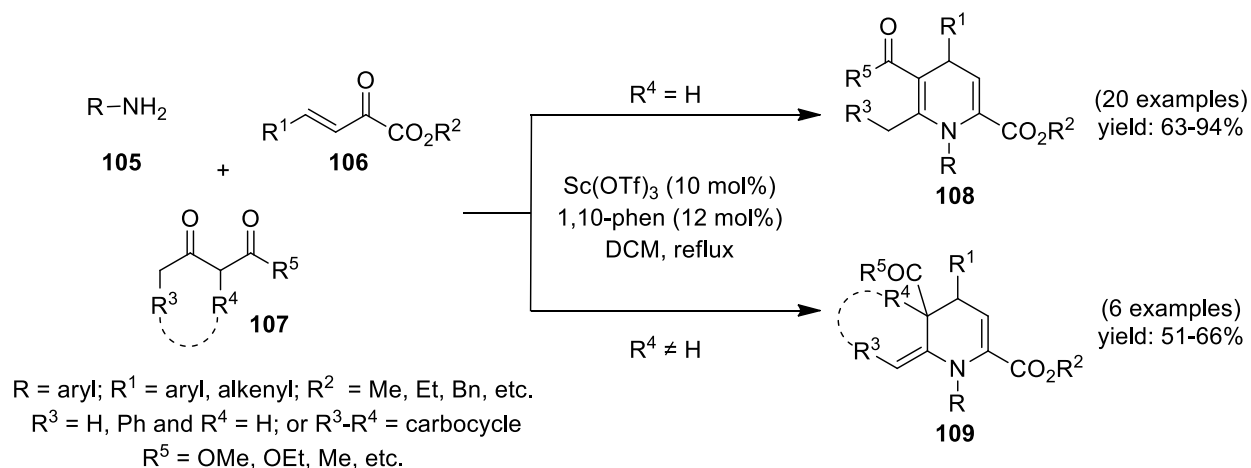


Scheme 30. Enantioselective Sc-catalyzed C-insertion.

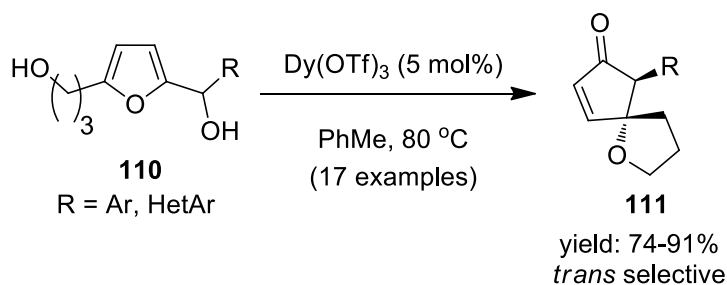
Highly substituted 1,4-dihydropyridines **108** and fused bicyclic tetrahydropyridines **109** can be prepared via a novel Sc(OTf)₃-catalyzed three-component coupling reaction of arylamines **105**, β,γ-unsaturated α-ketoesters **106**, and 1,3-dicarbonyl compounds **107** (Scheme 31).⁸² Notably, Cu(OTf)₂ did not affect the cyclization, and Zn(OTf)₂, Y(OTf)₃ and Yb(OTf)₃ were less efficient for this reaction, resulting in lower conversion. Prolonged reaction times did not show substantial yield improvement. On the other hand, addition of pyridine-based ligands resulted in increased conversion, presumably due to stabilization of metal complex intermediates. In a preliminary experiment, an asymmetric version of this transformation with (3*aR*,8*aR*)-indane-Pybox ligand lead to low enantioselectivity and moderate yield.⁸²

Application of dysprosium(III)-based Lewis acids in organic synthesis has been a subject of long-standing research interest of Read de Alaniz and his research group.⁸³ They reported several inter- and intramolecular variants of the aza-Piancatelli reaction, which were promoted by Dy(OTf)₃ and gave rise to a number of complex, highly-functionalized molecular architectures.⁸⁴⁻⁸⁶ A 2013 paper from the above-mentioned group disclosed an unprecedented Piancatelli rearrangement involving alcohols as nucleophiles.⁸⁷ The operationally simple reaction is catalyzed by Dy(OTf)₃ and proceeds in PhMe at 80 °C, affording structurally unique *trans*-substituted spirocyclic ether motif **111** (Scheme 32). It should be noted that the transformation

effects simultaneous construction of a fully substituted carbon center and a spirocycle, thus achieving exceptional atom economy in a single step.



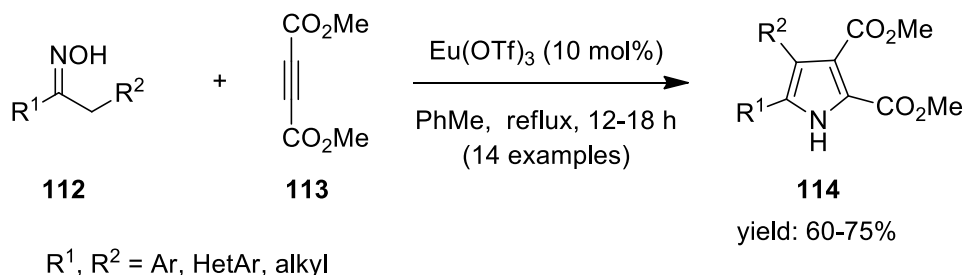
Scheme 31. $Sc(OTf)_3$ -catalyzed three-component cyclization.



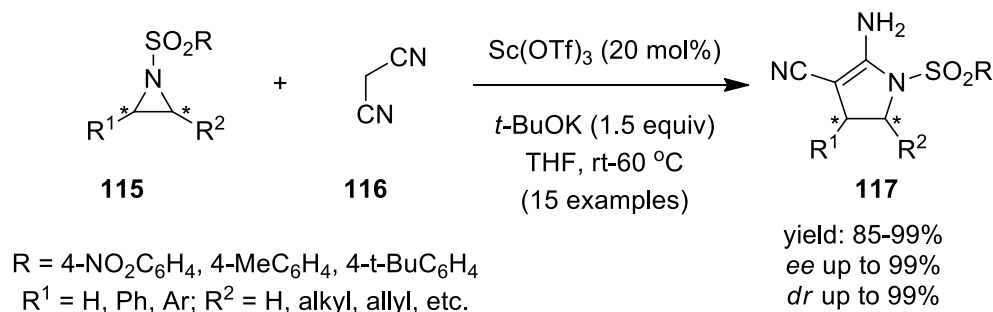
Scheme 32. Synthesis of spirocycles **111**.

During the development of a Lewis acid-catalyzed variant of the Trofimov reaction,⁸⁸ it was shown that among lanthanide(III) salts screened $Eu(OTf)_3$ offered superior catalytic activity and provided an efficient method for accessing polyfunctionalized pyrroles **114** (Scheme 33).⁸⁹ The $Eu(OTf)_3$ -promoted Trofimov pyrrole synthesis exhibited broad reaction scope with a wide range of aromatic, heteroaromatic and aliphatic side-chains tolerated.

An efficient and practical approach for the preparation of densely functionalized racemic and enantiopure 4,5-dihydropyrroles **117** was developed by Ghorai and co-workers.⁹⁰ Thus, N-activated aziridines **115** reacted with malononitrile **116** in the presence of $Sc(OTf)_3$ via a novel domino ring-opening cyclization (Scheme 34). Markedly, $Sc(OTf)_3$ additive was crucial for the activation of sulfonyl aziridine component **115** via a chelation process. The proposed mechanism proceeds via an S_N2 -type pathway, followed by intramolecular cyclization.



Scheme 33. Eu(OTf)₃-promoted pyrrole synthesis.



Scheme 34. Preparation of 4,5-dihydropyrroles **117** via Sc(OTf)₃-promoted cyclization.

3. Conclusions

This contribution has highlighted diverse features and unique efficiency of rare earth metal triflates for a vast number of cyclization and cycloaddition reactions. The great advantages of M(OTf)₃ reagents—their superior catalytic activity even in a presence of Lewis bases, low toxicity, easy handling, moisture and air stability, and possibility of recycling/reuse—have led to their widespread use in organic synthesis. This review will hopefully stimulate further application of rare-earth metal(III) triflates in synthesis, and the discovery of novel transformations catalyzed by these compounds will undoubtedly serve as the basis for a multitude of new and improved synthetic strategies and protocols.

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Author's Biography



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