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3 Rare earth metal-catalyzed multicomponent reactions

3.1 Introduction

Multicomponent reactions (MCRs) are one-pot synthetic processes that involve at least three commercially available or easily accessible substrates that combine together to produce a single product through cascade reactions [1]. MCRs are advantageous and popular because of their atom-economy and step-efficiency, which reduce waste generation. In particular, their ease of use and their adaptability to experimental techniques reveal their entries to a broad array of synthetic compounds over the multiple combination opportunities of coupling reagents. The Strecker reaction was the first ever reported example of such an MCR reaction in which α -aminonitriles were synthesized from aldehydes. Following Strecker's synthesis, the chemical community rapidly progressed to further carbonyl-based MCRs. The well-known aldehyde-based MCR is the Mannich reaction, which yields an iminium intermediate, which is obtained from formaldehyde and amines, either primary or secondary, which reacts with carbonyl compound to afford β -aminocarbonyls [2]; and the Biginelli reaction converts an aldehyde, a β -ketoester, and urea into dihydropyrimidones [3]. Simultaneously, isocyanide-based MCRs are also developed. The first isocyanide-based MCRs report, Passerini reaction [4], was published in 1921 and rapidly attained prominence in the pharmaceutical sector. The Ugi condensation [5], another foremost isocyanide-based MCR that consists of an aldehyde, an amine, a carboxylic acid, and an isocyanide, allows for the hasty assembly of libraries of α -aminoacyl amide derivatives, making it useful for drug development.

Nowadays, the overall demand for practical and effective synthetic methods propels new research and encourages the creative rethinking of well-established ideas. The desire for sustainable energy and atom-efficient reactions are driving an increase in the demand for Lewis acid-catalyzed multicomponent reaction methods, which open up new avenues in synthetic organic chemistry. Rare earth metal-induced MCRs

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are one of the Lewis acid catalysts that are currently developing, although significant advancements are anticipated in this area shortly.

3.2 Various organic synthesis using rare earth metals as catalysts

3.2.1 Synthesis of substituted pyrroles derivatives

Pyrrole is an important constituent of porphyrin, chlorophyll, and bile pigment. It is also a main scaffold of amino acids such as proline and hydroxyproline. In addition to these prevalent compounds, pyrrole structural fragments are particularly found in natural products of marine origin. The most prominent and well-known method for the preparation of pyrrole is Paal-Knorr synthesis [6, 7]. Depending on the importance of pyrrole moiety, several scientific communities have showcased various synthetic protocols [8, 9] for the preparation of pyrrole scaffold.

Shiraishi and co-workers [10] developed an efficient and mild MCR protocol for the synthesis of multi-substituted pyrrole compounds (**4**) (Figure 3.1). The protocol involves the reaction of rare earth metal SmI_2 or SmCl_3 -catalyzed coupling of amines (**1**), aldehydes (**2**), and nitroalkane (**3**).

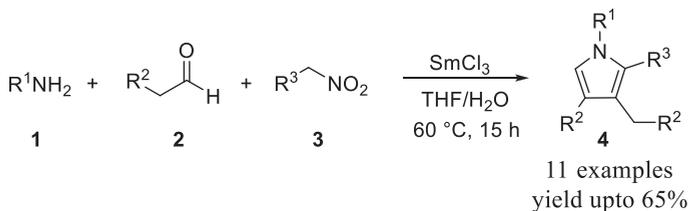


Figure 3.1: Synthesis of samarium catalyzed pyrroles through MCR.

This MCR sequence involves the reaction of amine (**1**) and aldehyde (**2**) to form imine (**A**), which undergoes aldol condensation with aldehyde (**2**) in the presence of samarium catalyst to give α , β -unsaturated imine (**B**). The obtained α , β -unsaturated imine (**B**) reacts with nitroalkane (**3**) under heating, following the Michael addition adduct (**C**), proton abstraction adduct (**D**), cyclization, and isomerization (**E**), giving multi-substituted pyrrole derivatives (**4**) (Figure 3.2). The present protocol is suitable for aldimines, but is a limitation for ketimines obtained from the condensation of ketones and amines.

Encouraged by the synthesis of samarium (III)-catalyzed pyrroles, the same group developed a diversified protocol for the regioselective construction of pyrroles (**7**) by the reaction of nitroalkenes (**6**) and imines (**8**) under samarium catalysis (Figure 3.3) [11]. In this protocol, a wide range of nitro alkenes (**6**) (obtained from amines (**1**) and

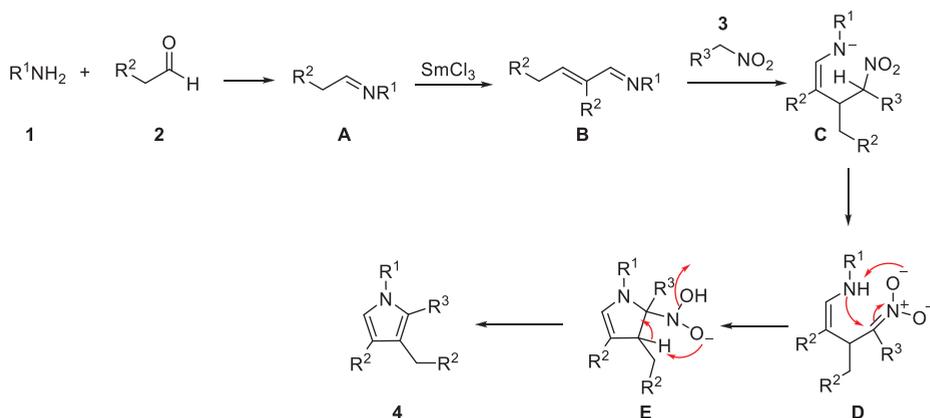


Figure 3.2: Reaction mechanism of samarium (III)-catalyzed pyrroles synthesis through MCR.

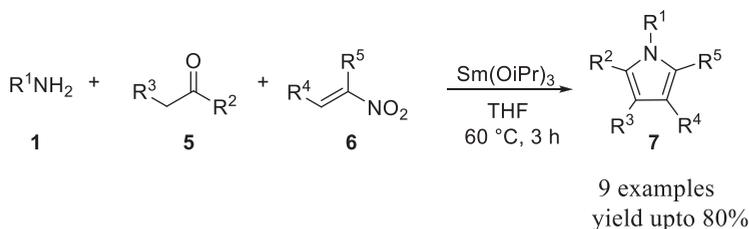


Figure 3.3: Synthesis of pyrroles via samarium-catalyzed MCRs.

an aldehyde or ketones (5) (Figure 3.4) and imines (8) were combined to generate substituted pyrroles (7) as well as fused pyrrole derivatives in moderate to good yields. The yield of the pyrrole derivative was affected by the substituent alkyl group attached to the nitrogen atom of imines. As the bulkiness of the alkyl group increases, yield of the corresponding pyrrole derivative decreases.

3.2.2 Synthesis of functionalized dihydropyrimidine derivatives via Biginelli condensation

Dihydropyrimidines (DHPMs) are a class of nitrogen-containing complexes heterocyclic scaffolds that are present in several marine alkaloids (such as crambine and batzelladine) [12]. In addition, it has been found that they are effective HIV gp-120CD4 inhibitors [13]. Besides, a number of multi-functionalized dihydropyrimidines also reveal antitumor [14], antibacterial [15], antiviral [16], and anti-inflammatory properties [17] in addition to having exceptional pharmacological effectiveness. Despite many

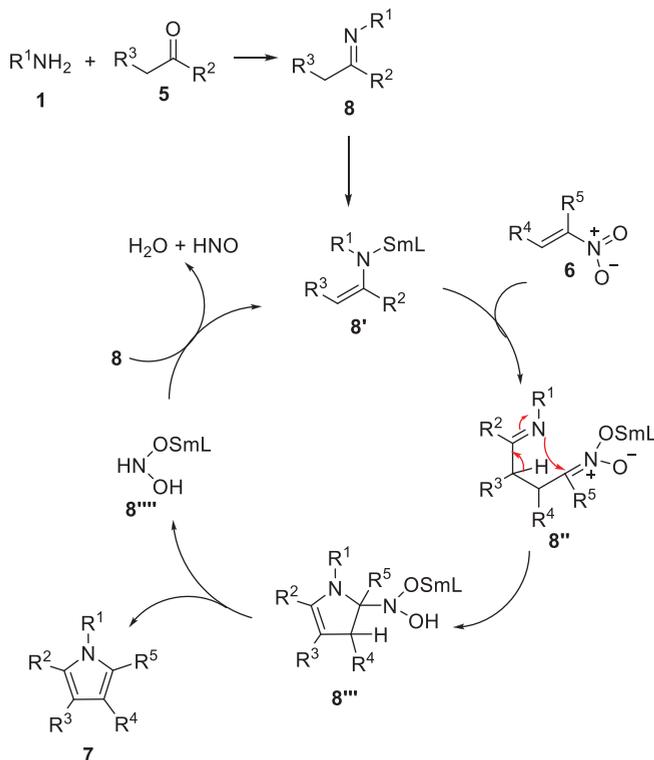


Figure 3.4: Reaction mechanism of samarium (III)-catalyzed pyrroles synthesis through MCR.

approaches that have materialized [18–26], still it requires mild protocols for the construction of dihydropyrimidine derivatives.

Ma and co-workers [27] reported an highly efficient Yb(OTf)₃-mediated multicomponent reaction of aldehydes (9), urea (10), and β-ketoesters (11), via the Biginelli reaction for the preparation of dihydropyrimidines (12) under a solvent-free environment at 100 °C (Figure 3.5). Replacing β-ketoesters with 1,3-diketones, the reaction proceeds smoothly, furnishing dihydropyrimidines.

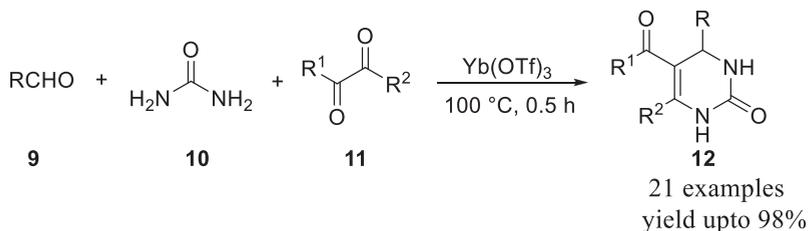


Figure 3.5: Synthesis of dihydropyrimidines via Yb(OTf)₃-catalyzed MCRs.

A representative procedure for the synthesis of pyrimidinones (**15**) was provided by Narasaiah et al. [28] via multicomponent reaction of urea (**10**), β -ketoesters (**13**), and aldehydes (**14**) under samarium catalysis (Figure 3.6). The present protocol involves the elimination of tedious work-up process for the purification of products. Purification of products encompasses the removal of the solvent under reduced pressure. The resulting residue was mixed with crushed ice for a while, filtered, dried, and purified by recrystallization from methanol.

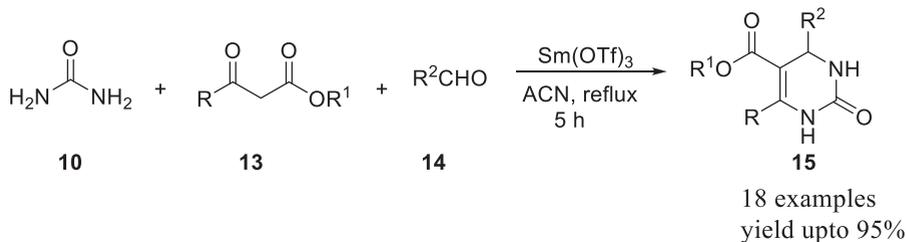


Figure 3.6: Synthesis of dihydropyrimidines via $\text{Sm}(\text{OTf})_3$ -catalyzed MCRs.

Complex optically active dihydropyrimidines (**17**) have been generated utilizing a highly enantioselective multicomponent reactions using Biginelli condensation, and employing a recyclable asymmetric $\text{Yb}(\text{OTf})_3$ catalyst with a new hexadentate chiral ligand (**L**) (Figure 3.7) [29]. The reaction produces high yields of dihydropyrimidines with decent enantioselectivity (Figure 3.7–I). A suggested transition state model assigned the product's absolute configuration. The acylimine intermediate produced in situ might coordinate with the Yb atom. The pyridyl group shielded the coordinated acylimine's *si*-face, allowing the enol ester to attack as nucleophile from the *re*-face.

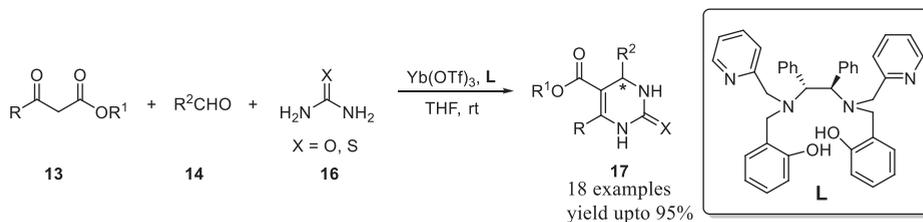


Figure 3.7: Asymmetric synthesis of dihydropyrimidines via $\text{Yb}(\text{OTf})_3$ -catalyzed MCRs.

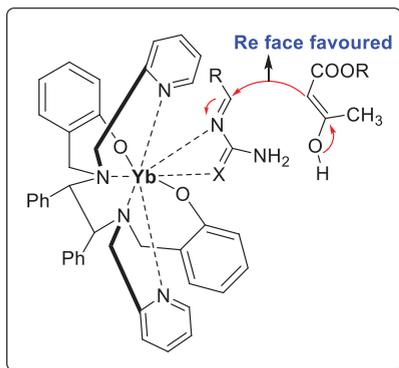


Figure 3.7-I: Transition state model showing *Re*-face attack of enol.

3.2.3 Synthesis of nitrogen containing compounds via Ugi reaction

Ugi reaction constitutes 4-component coupling (4CC) of amines, aldehydes, carboxylic acid, and isonitriles for the construction of libraries of nitrogen-containing compounds [30]. Keung and co-workers [31] have demonstrated scandium triflate-catalyzed variable Ugi three component coupling reaction for the synthesis of α -aminoamidine derivatives (Figure 3.8). This new method revealed a novel route for the preparation of imidopyrazine (24) (Figure 3.9) and hydantoin imide (27) (Figure 3.10).

Okandeji et al. [32] reported a high yielding multicomponent Ugi reaction using sub-stoichiometric amounts of ytterbium and scandium triflate catalysts for the production of α -acylamino carboxamide (30 and 31) (Figure 3.11). The activation of the imine intermediate of this multicomponent reaction is principally responsible for the

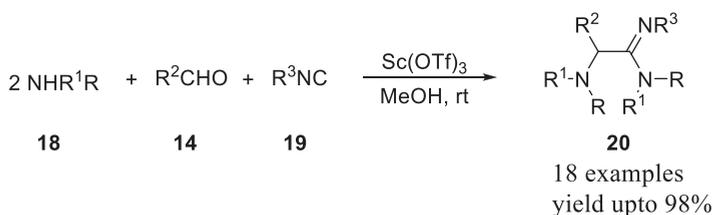


Figure 3.8: Sc(OTf)₃-mediated variable MCRs for constructing α -aminoamidine.

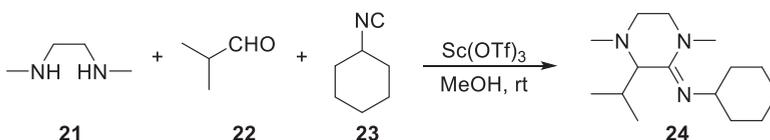


Figure 3.9: Sc(OTf)₃-mediated variable MCRs for assembling imidopyrazine.

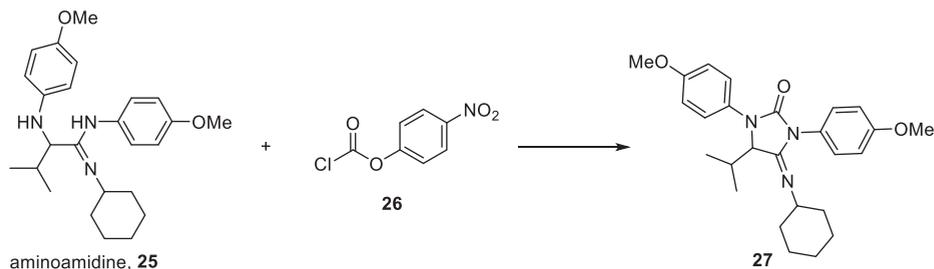


Figure 3.10: $\text{Sc}(\text{OTf})_3$ -mediated hydantoin imide preparation via MCRs.

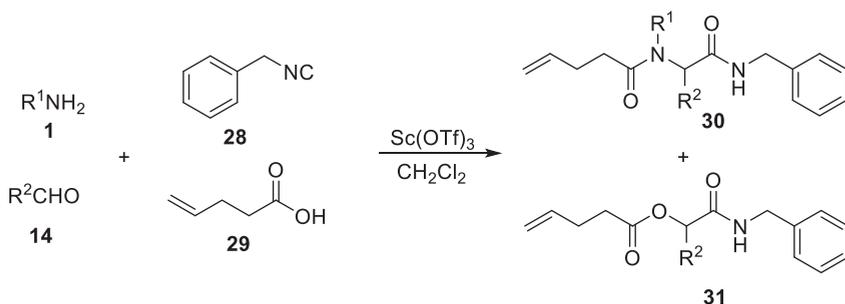


Figure 3.11: $\text{Sc}(\text{OTf})_3$ -catalyzed Ugi4CC for the synthesis of α -acylamino carboxamide.

improvement in product yield. The possibility of realizing catalytic asymmetric Ugi 4CC reactions is encouraged by the apparent mechanism of catalysis, the striking variations in yield between the catalyzed and uncatalyzed reactions, and the accessibility of chiral $\text{Sc}(\text{III})$ complexes.

3.2.4 Synthesis of oxazolidinones

In 2016, Xu et al. [33] reported a three component coupling of propylene oxide (PO) (32), carbon dioxide (33), and substituted anilines (34) for the synthesis of oxazolidinones (35) under rare earth metal catalyst stabilized by amine-bridged tri-(phenolato) ligands (L1-L6) (Figure 3.12). In this reaction, a series of rare earth metal catalyst stabilized by amine-bridged tri-(phenolato) ligands complexes were prepared and studied for their catalytic efficiency (Figure 3.13). Complexes with electron-withdrawing group attached to the aromatic ring increase the acidity of the rare earth metal, which in turn enhances the activity of substrates, leading to quantitative yields of oxazolidinones (35). Excess ratio of PO (32)-to-aniline (34) was essential for the significant increase in the yield of the product. Ortho-substituted, irrespective of electron-donation or withdrawing anilines, and aliphatic amines were unsuitable for this conversion.

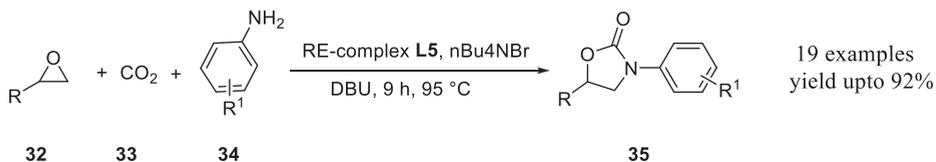


Figure 3.12: Nd-complex-catalyzed 3CC for the synthesis of oxazolidinones.

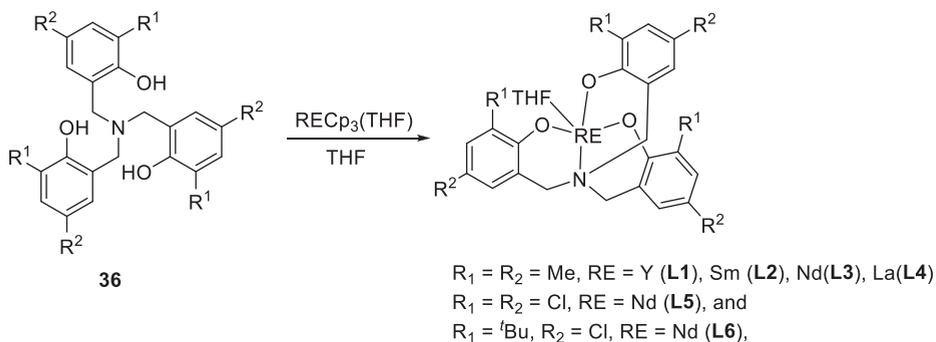


Figure 3.13: Synthesis of rare earth metal catalyst stabilized by amine-bridged tri-(phenolato) ligand complexes.

Pioneering work on 3 CC reactions for the synthesis of oxazolidinones provided the first report of 3-aryloxazolidinone (35) synthesis from easily available three component coupling of epoxide (32), aniline (34), and dialkyl carbonate (37) (ratio 2:1:2), under solvent-free rare earth metal amide catalysis (Figure 3.14) [34]. In addition, the reaction produces MeOH as the byproduct. The reaction is limited to monosubstituted epoxides, whereas in the reaction with vicinal disubstituted epoxides, the reaction is sluggish or does not take place. Catalytic efficiency of metal amides decreases with decrease in ionic radii of rare earth metal ions.

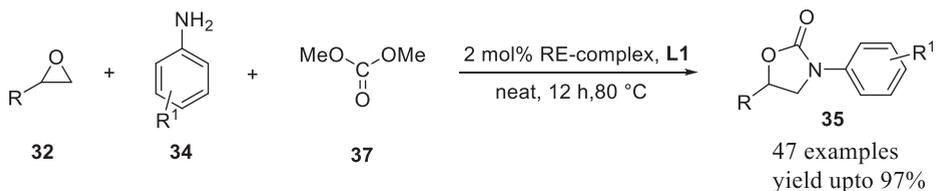


Figure 3.14: Synthesis of oxazolidinones, catalyzed by rare earth metal amide.

Ceric ammonium nitrate (CAN)-mediated synthesis of Betti bases (40) [35] from commercially available substrates *viz.* aryl and alkylamines (34), substituted benzaldehydes (38), and 2-naphthol (39), (1:1.2:1) was reported by Mekheimer et al. [36] (Figure 3.15).

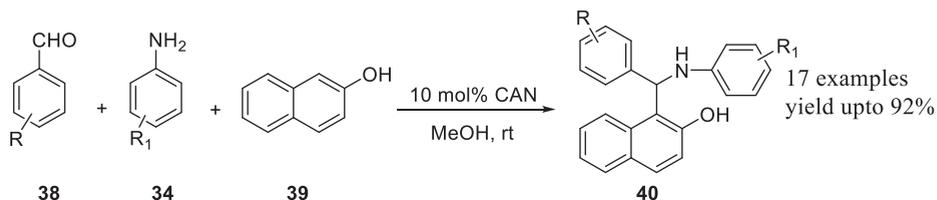


Figure 3.15: CAN-mediated synthesis of Betti base.

The reaction works well in ambient conditions with moderate-to-good yields in methanol. When the methanol was replaced by water, the reaction furnishes Schiff base, instead of betti base.

3.2.5 Synthesis of 3-aminoimidazoles

Rapid and efficient microwave-assisted 3 component coupling (3 CC) Ugi reaction of amidine (**41**), isocyanides (**19**), and aldehydes (**14**) for the synthesis of libraries of 3-aminoimidazoles (**42**), catalyzed by scandium triflate in methanol was described by Ireland and co-workers [37] (Figure 3.16). A variety of combinations of amidine (**41**), aldehydes (**14**), and isocyanides (**19**) undergo coupling to give a wide range of aminoimidazoles (**42**). The reaction was completed in a very short span of 10 min.



Figure 3.16: Microwave-assisted $\text{Sc}(\text{OTf})_3$ -catalyzed 3 CC Ugi reaction for the formation of 3-aminoimidazoles.

Hulme et al. [38] proposed a related 3 component coupling reaction for the synthesis of 3-aminoimidazopyridines (**45**) under microwave irradiation, catalyzed by scandium triflate using simply accessible reactants – 2-aminopyridine (**43**), trimethylsilylcyaniide (**44**), (TMSCN, anisonitrile equivalent), and aldehyde (**14**) in methanol (Figure 3.17).

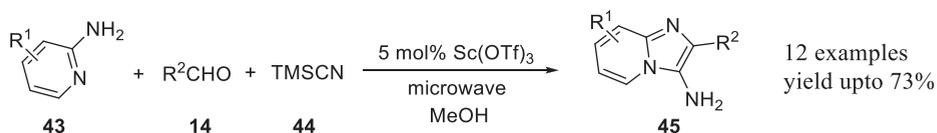


Figure 3.17: $\text{Sc}(\text{OTf})_3$ -catalyzed formation of 3-aminoimidazopyridines under microwave conditions.

3.2.6 Synthesis of quinoline derivatives via Pavarov reaction

In 2011, Vicente-García et al. [39] reported an effective $\text{Sc}(\text{OTf})_3$ -mediated domino Pavarov reaction [40] for the synthesis of diverse heterocycle tetrahydro-quinoline derivatives (**47**) by employing oxa-, thia-, and imidazolones as a novel class of electron-rich olefin partner (**46**) (dienophile) interaction with anilines (**34**) and aldehydes (**14**) (Figure 3.18). The use of a new class of olefin (dienophile) opens up a new direction for the construction of structural diversity of tetrahydroquinoline derivatives. The obtained MCR adducts were conveniently oxidized to yield the corresponding quinolones (**48**).

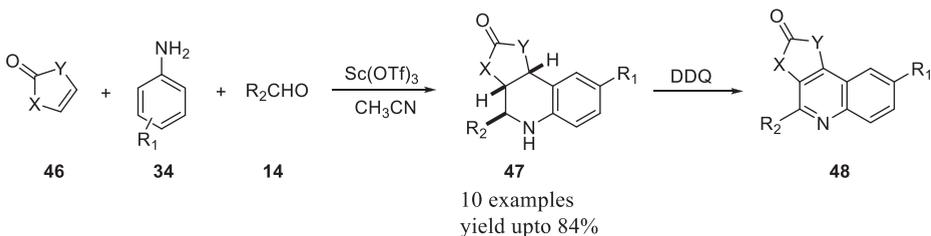


Figure 3.18: $\text{Sc}(\text{OTf})_3$ -catalyzed multicomponent Pavarov reaction toward the construction of quinolone derivatives.

Dhanapal et al. [41] reported scandium(III) triflate-catalyzed Pavarov reaction between *para*-substituted anilines (**34**), vinyl pyrrolidone (**49**), and phenanthrene-9-carbaldehyde (**50**) for the synthesis of quinolones (**51**) as fluorescence probes for bacteria detection (Figure 3.19). The reaction was conducted at room temperature using $\text{Sc}(\text{OTf})_3$ in acetonitrile to produce *cis*-2-(phenanthren-10-yl)-4-(2-oxopyrrolin-1-yl)tetrahydroquinoline intermediates that could then be further oxidized with DDQ in refluxing methylbenzene (toluene) to produce the corresponding quinoline derivatives (**51**).

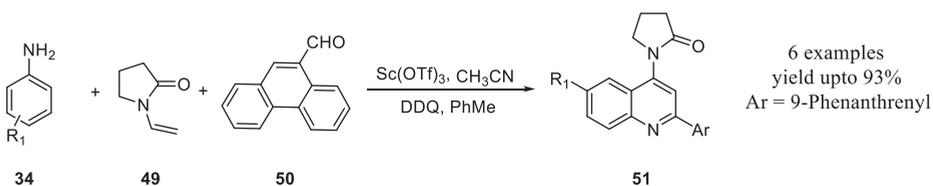


Figure 3.19: Pavarov multicomponent assembly of quinolone catalyzed by $\text{Sc}(\text{OTf})_3$.

3.3 Conclusions

In conclusion, we have showcased the synthetic utility of rare earth metal complexes toward the synthesis of carbon and nitrogen heterocyclic compounds. Albeit, rare earth metal complexes are expensive compared to standard transition metal complexes, they are frequently employed in sub-stoichiometric amounts. It is significant to note that the rare earth metal complexes are active in aqueous environment, eliminating the need for laborious drying process of the reaction conditions. Despite great contributions made in multicomponent reaction by using rare earth metal complexes, there is still room for further development and applications of water-tolerant rare earth complexes in sustainable MCR methodologies. It is also important to encourage the research community to develop advanced methods for the recovery and recycling of rare earth metal complexes. Additionally, investigation on the sequential MCRs with rare earth complexes would permit chemists to construct heterocyclic scaffolds with great complexity and biological profiles.

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