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Review

Catalytic Efficiency of Primary α-Amino Amides as Multifunctional Organocatalysts in Recent Asymmetric Organic Transformations

Ummareddy Venkata Subba Reddy [1,*], Bheemreddy Anusha [2], Zubeda Begum [3], Chigusa Seki [3], Yuko Okuyama [4], Michio Tokiwa [5], Suguru Tokiwa [5], Mitsuhiro Takeshita [5] and Hiroto Nakano [3,*]

1 Department of Chemistry, DRG Government Degree College, Tadepalligudem, West Godavari, Andhra Pradesh 534166, India
2 Department of Chemistry, Silver Jubilee Government College (A), Cluster University, Kurnool, Andhra Pradesh 518002, India
3 Division of Sustainable and Environmental Engineering, Graduate School of Engineering, Muroran Institute of Technology, 27-1 Mizumoto, Muroran 050-8585, Japan
4 Faculty of Pharmaceutical Sciences, Tohoku Medical and Pharmaceutical University, 4-4-1, Sendai 981-8558, Japan
5 Tokiwakai Group, 62 Numajiri Tsuduri-Chou Uchigo, Iwaki 973-8053, Japan
* Correspondence: ummareddyvsr@gmail.com (U.V.S.R.); catanaka@mmm.muroran-it.ac.jp (H.N.)

Abstract: Chiral primary α-amino amides, consisting of an adjacent enamine bonding site (Bronsted base site), a hydrogen bonding site (Bronsted acid site), and flexible bulky substituent groups to modify the steric factor, are proving to be extremely valuable bifunctional organocatalysts for a wide range of asymmetric organic transformations. Primary α-amino amides are less expensive alternatives to other primary amino organocatalysts, such as chiral diamines and cinchona-alkaloid-derived primary amines, as they are easy to synthesize, air-stable, and allow for the incorporation of a variety of functional groups. In recent years, we have demonstrated the catalytic use of simple primary α-amino amides and their derivatives as organocatalysts for the aldol reaction, Strecker reaction, Michael tandem reaction, allylation of aldehydes, reduction of N-Aryl mines, opening of epoxides, hydrosilylation, asymmetric hydrogen transfer, and N-specific nitrosobenzene reaction with aldehydes.

Keywords: asymmetric organic transformations; organocatalysis; primary α-amino amides; bifunctional organocatalysts; enamine bonding

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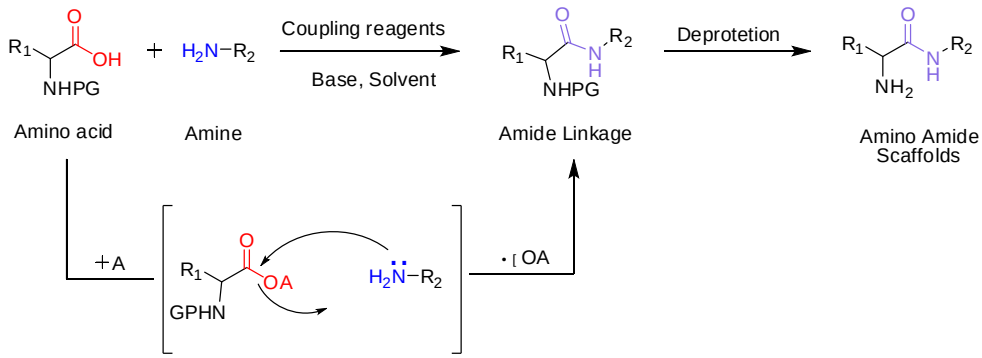
1. Introduction

Bifunctional catalysts have low molecular weight, two distinct functional groups, and a chiral scaffold. Hence, these catalysts can cause additional reactivity and/or selectivity into various reactions. The reactions are classically polar addition reactions of pro-nucleophiles and electrophiles in which simple, low-cost starting materials are ideally converted into highly selective specified products as a result of the bifunctional catalyst system. Most bifunctional catalysts with Lewis or Brønsted basic functionality and a tunable hydrogen bonding site suitably positioned over a chiral scaffold can be easily tuned to optimize reactivity and selectivity in synthetically relevant reactions, allowing for high reaction rates and excellent stereoselectivity.

Compared to single functional group catalysts, the cooperative effect of the two complimentary functional groups can lead to new reactivity and stereo control in previously difficult or unexpected processes. The development of simple bifunctional catalysts has been a profitable and active topic of research in chemical synthesis during the last few decades [1–5]. Along with metal–organic cooperative asymmetric catalysts [6–9], a variety of bifunctional organocatalysts, including H-bond donors, as well as Lewis/Brønsted basic, nucleophilic, acidic functional groups (such as proline and its analogues [10–12], ammonium salts of diamine [13–15], cinchona alkaloids and derivatives [16–19], primary β-amino alcohols [20], thiourea derivatives [21–23], amino squaramide derivatives [24–27], phosphoric

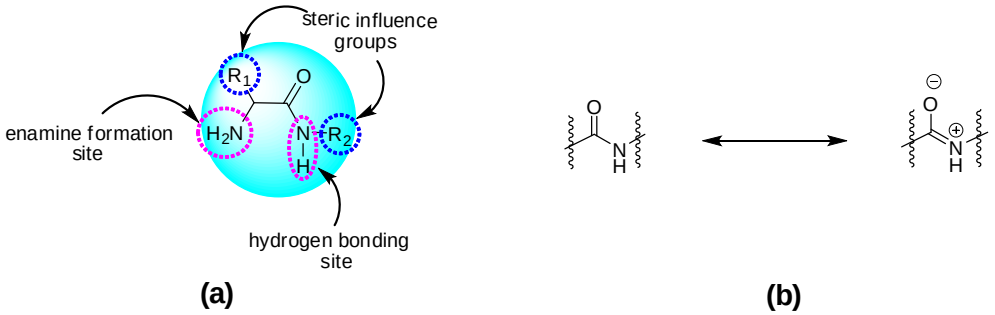
acid derivatives [28,29], H-bonding phase-transfer catalysts [30–32], and peptides [33,34]) have been developed and tested in asymmetric organic transformations to investigate their catalytic activity.

Owing to their ease of synthesis and stability in air, amino amides have emerged as affordable and self-sufficient multifunctional chiral templates in enantioselective organocatalysis in recent years. Amino amide structures can be easily generated from commercially available amino acids and free amines using well-known coupling procedures (Scheme 1). A carboxylic acid is activated by an activating (A) group, followed by nucleophilic displacement by a free amine in the presence of a coupling reagent and a base. The necessary amino amide scaffolds can then be created through easy deprotection of the coupling product's amine function.



Scheme 1. A conventional approach for construction of simple amino amide scaffolds.

These simple amino amide scaffolds possessing free amine and amide function can activate the reactant molecules through the enamine bonding site (acting as Brønsted base) and hydrogen bonding site (acting as Brønsted acid). Alternatively, the free amino group can also cause hydrogen bonding in the presence of external usage of Lewis acid through the formation of ammonium salt (Scheme 2a). The flexible substituent groups R_1 and R_2 can acts as steric factors to shield the one enantiotopic face of reactant molecules. This facility could enhance the catalytic activity of this class of scaffolds.



Scheme 2. (**a**) Multifunctional activity of amino amide scaffolds. (**b**) Resonance structure of amide bond.

Owing to the strong electronegativity of the oxygen atom of the carbonyl function, the lone-pair electrons in the adjacent positioned nitrogen atom of the amide bond are delocalized via resonance (Scheme 2b). Because the C=O bond has a higher dipole than the N=C bond, amides can operate as H-bond acceptors. The presence of N-H dipoles in primary and secondary amides allows them to function as H-bond donors as well. Owing to the favorable constructional properties of amino-amide-based bifunctional organocatalysts (such as easy synthesis, high polarity, stability in air, conformational diversity, their wide potential for steric site alteration, and their ability to be used as iminium bond sources and hydrogen bond sources), this class of catalysts is becoming increasingly popular with organic chemists in the field of asymmetric organic synthesis. Taking advantage of these benefits, various amino amide-based chiral organocatalysts have been created and tested for catalytic activity in a variety of processes in recent years.

To date, only one review has been reported on the catalytic competence of amino-amide-based organocatalysts by Xiaoming Feng et al. in 2009 [35], and Panday discussed proline amides as organocatalysts as part of his review of proline derivatives in 2011 [36]. In 2019, Surendra Singh et al. [37] reported the catalytic effectiveness of prolinamide and its derivatives using asymmetric methods. Along with prolinamide, a number of other simple amino amides have been created in recent years to examine their impact as bifunctional organocatalysts in asymmetric organic synthesis.

It is always a difficult task to find simple organic compounds and use them as independent chiral agents in asymmetric synthesis. Recently, we investigated the catalytic activity of simple β-amino alcohols as organocatalysts in asymmetric organic synthesis [20]. In this article, we report on the catalytic activity of simple amino-amide-based bifunctional asymmetric organocatalysts (from 2011 to date, excluding prolinamide) in valuable chemical transformations. Recently developed amino amide organocatalysts are exemplified as general base and general acid activation patterns through both covalent and noncovalent modes of interaction with the substrate in various organic asymmetric transformations, such as aldol reaction, Strecker reaction, Michael tandem reaction, allylation of aldehydes, reduction of N-Aryl imines, opening of epoxides, hydrosilylation, asymmetric transfer of hydrogen, and N-specific reaction of nitrosobenzene (Figure 1).

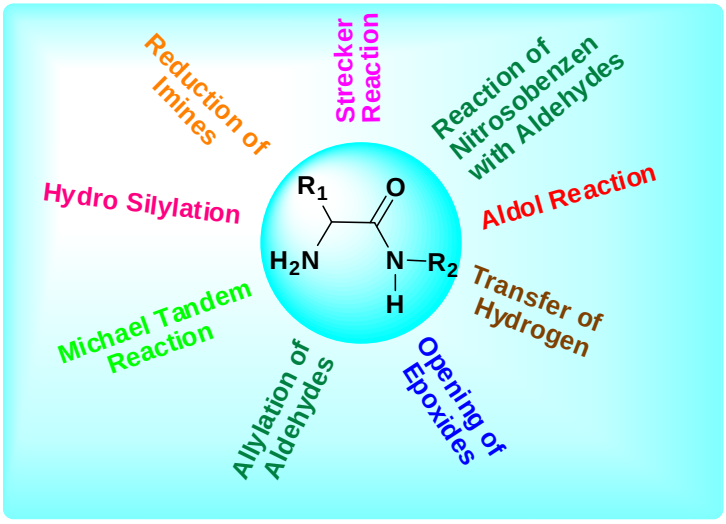


Figure 1. Catalytic efficiency of primary α-amino amides.

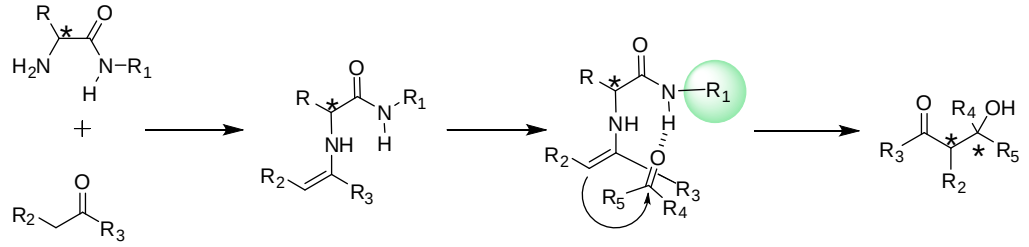
2. Primary α-Amino-Amide-Catalyzed Asymmetric Organic Transformations

2.1. Asymmetric Aldol Reaction

In current synthetic organic chemistry, the aldol reaction has established itself as one of the most powerful carbon–carbon bond-forming reactions [38,39]. It provides a complete atom-economic approach to β-hydroxyl carbonyls, which are used in various value-added process, such as the manufacturing of bulk and fine chemicals, as well as the preparation of biologically active compounds [40–44]. As a result, the development of asymmetric catalysis for aldol processes utilizing effective catalysts has been extensively researched. Since reports of L-proline-catalyzed intramolecular aldol reactions in the 1970s [45,46] and the development of proline-catalyzed asymmetric direct aldol reactions reported by List et al. in 2000 [47,48], a large number of proline-derived organocatalysts, such as proline analogues [49–51], acyclic amino acids [52–54], proline thioamides [55–57], sulphonamides [58–60], chiral amines [61–63], and organic salts [64–66], have been developed for their catalytic activity relating to direct asymmetric aldol reaction.

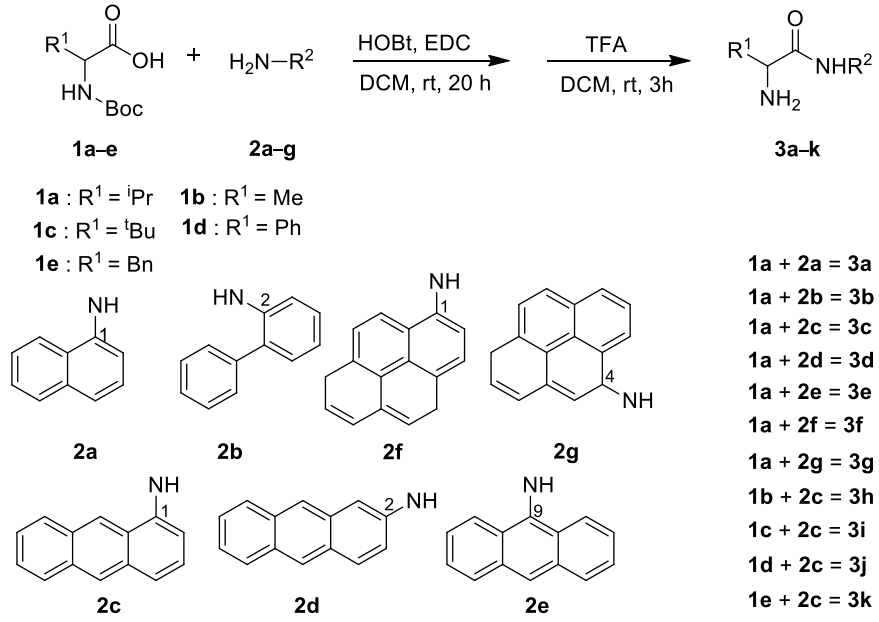
Subsequently, a variety of bifunctional amino-amide-based organocatalysts were created for the asymmetric aldol reaction. Enamine is produced in this catalysis by the reaction of a carbonyl function with amine, whereas hydrogen bonding between the N-H of the amide and the acceptor is required for asymmetric induction (Scheme 3). The primary

focus of this review is the design and synthesis of various bifunctional catalysts based on the structure of amino amide bond, as well as the importance of N-H bonds in direct asymmetric aldol processes. The various substituent groups (R_1 group in Scheme 3) were introduced on the N atom of the amide function by increasing the acidity of the proton of the amide, forming a strong hydrogen bond with the aldol acceptor and, by steric induction, controlling the approach of the enamine to the aldol acceptor.



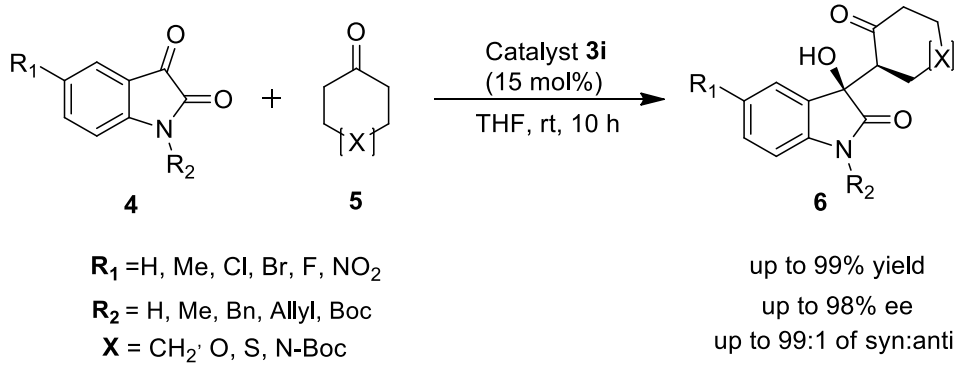
Scheme 3. Coordination of amino amide bifunctional catalysts in direct intermolecular aldol reactions.

We designed and synthesized simple amino amide catalysts from their corresponding amino acids and simple amines using a well-established coupling method with 1-hydroxybenzotriazole (HOBt) and 1-ethyl-3-[3-(dimethylamino) propyl] carbodiimide (EDC) as coupling agents [67], owing to the prominence of the amino amide moiety as a bifunctional, self-sufficient organocatalyst that activates the reactants through covalent bond (Scheme 4) [68].



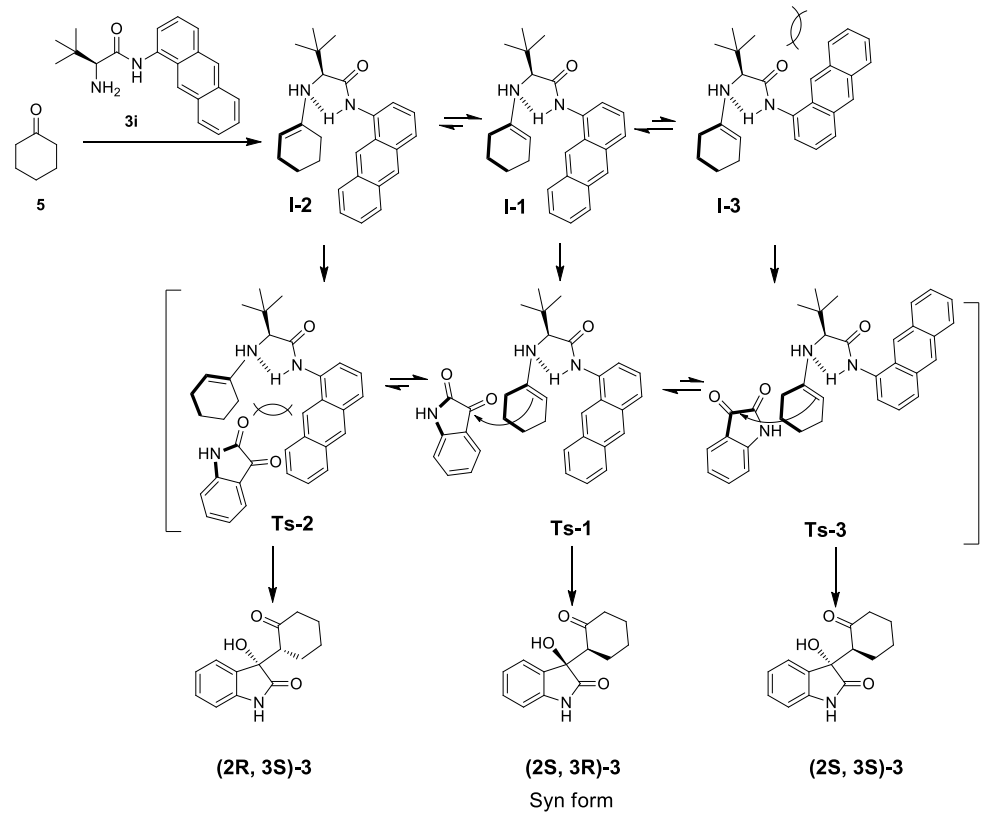
Scheme 4. Synthesis of amino amide catalysts **3a**–**k**.

We predicted that our synthesized catalysts (**3a–k**) would have a flexible, bulky amide polycyclic aromatic hydrocarbon group, as well as an enamine site and a hydrogen bonding site. These sites would protect one enantiotopic enamine face from cyclic and acyclic ketones to produce high enantioselectivity. These chiral amino amides (**3a–k**) were tested as catalysts in the aldol reaction of isatins with various cyclic ketones [69]. We discovered that the related aldol adducts had outstanding chemical and optical yields (Scheme 5). Among the known catalysts, catalyst **3i**, with a *t*-butyl group in the α position and a 1-anthracenyl group on the amide nitrogen, produces the optimal results.



Scheme 5. Isatin–cycloketone aldol reaction with amino amides as organocatalysts.

Scheme 6 represents the proposed reaction mechanism for this process. The enamine intermediate is formed by the condensation of catalyst **3i** with **5**, which is conformationally locked by the H-bonding interaction between the enamine N atom and the catalyst's amide H atom. The enamine intermediate can exist as **I-1**, **I-2**, or **I-3**; among these three conceivable enamine intermediates, **I-1** has low energy and stable confirmation, as proven by energy calculations of the three intermediates (**I-1**–**3**) at the theoretical levels of B3LYP/6-311++G(d,2p)/B3LYP/6-31+G(d) (Figure 2) [69]. This was also proven by the basis of isomer **I-1**–**3** and isatin **4** boundary molecular orbital energies. As a result, the matching aldol product was produced with outstanding enantioselectivity and diastereoselectivity via intermediate **I-1**.



Scheme 6. Proposed mechanism of aldol reaction of isatin with cyclic ketones.

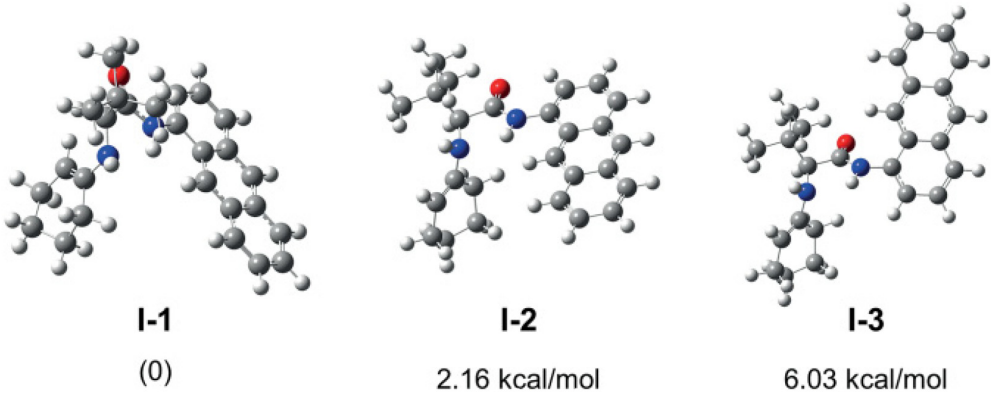
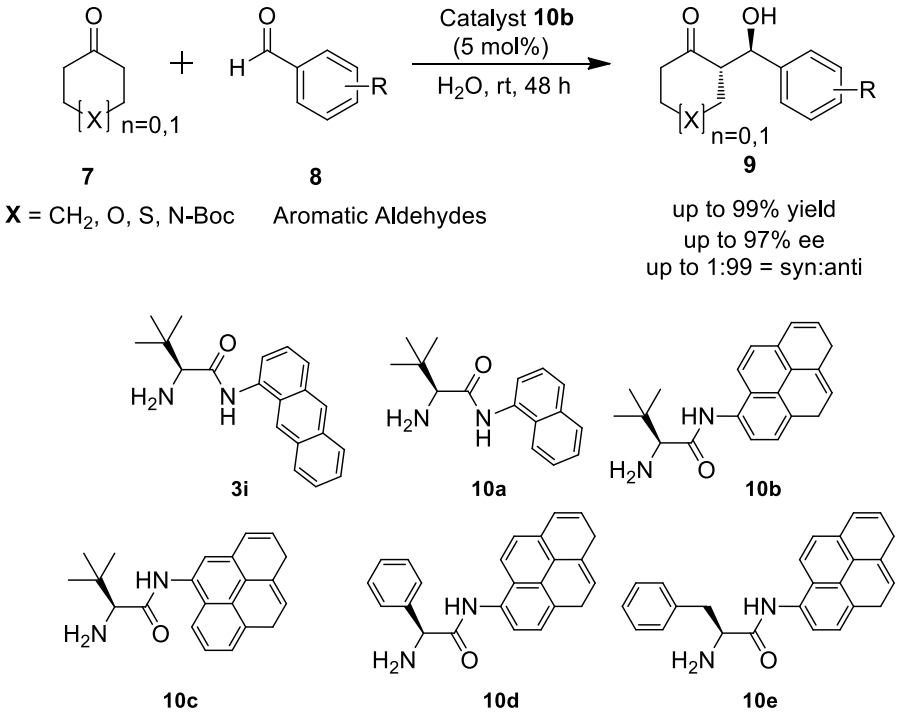


Figure 2. Structures and relative energies of intermediates **I-1–3** calculated at the B3LYP/6-311++G(d,2p)//B3LYP/6-31+G(d) levels of theory. Energy values are compared to the lowest-energy isomer **I-1**. Reprinted with permission from Ref. [69]. Copyright 2016, John Wiley and Sons.

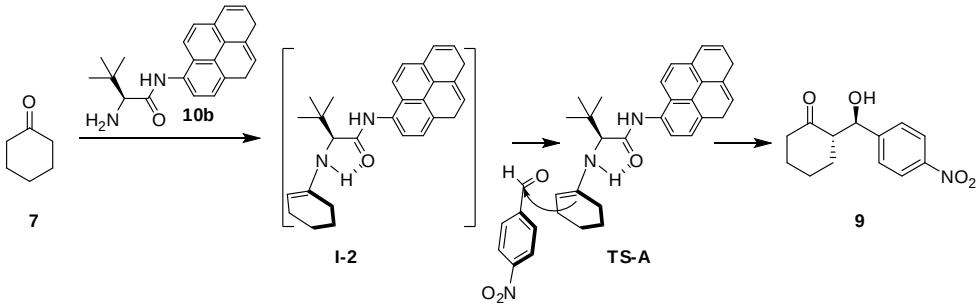
Inspired by these findings and using the bifunctional catalytic efficiency of these simple amino amide skeletons, we then investigated the aldol reaction of cyclic ketones with aromatic aldehydes [70]. Among all screened catalysts, catalyst **10b** demonstrated the most efficient catalytic activity in the crossed aldol reaction of various cyclic ketones (**7**) with various substituted aromatic aldehydes (**8**) to yield the corresponding anti-aldol adducts (**9**) with good to excellent chemical yields and stereoselectivities (up to 99%, up to *syn*:*anti* 1:99, up to 97% *ee*) with a low-loading catalyst (5 mol%) (Scheme 7) [70].



Scheme 7. Aldol reaction of ketones with aromatic aldehydes using amino amides as catalysts.

The following reaction course was proposed (Scheme 8). The bonding connection between the hydrogen atom on the nitrogen atom of the enamine segment and the amide carbonyl group in organocatalyst species fixes the enamine intermediate **I-2** formed by the condensation of organocatalyst **10b** with **7**. As a result, 4-nitrobenzaldehyde (**8**) could approach the stable enamine intermediate (**I-2**) in a variety of ways to form different transition states, but **TS-A** has the least steric interaction and stable confirmation to yield the *anti*-aldol product (**9**). These were confirmed using calculation studies (Figure 3) and

by calculating the energies and coefficients of their frontier orbitals (**8** and **I-2**) obtained by DFT at the B3LYP/6- 31G(d) level (Figure 4) [70].



Scheme 8. Reaction course of aldol reaction catalyzed by an amino amide catalyst.

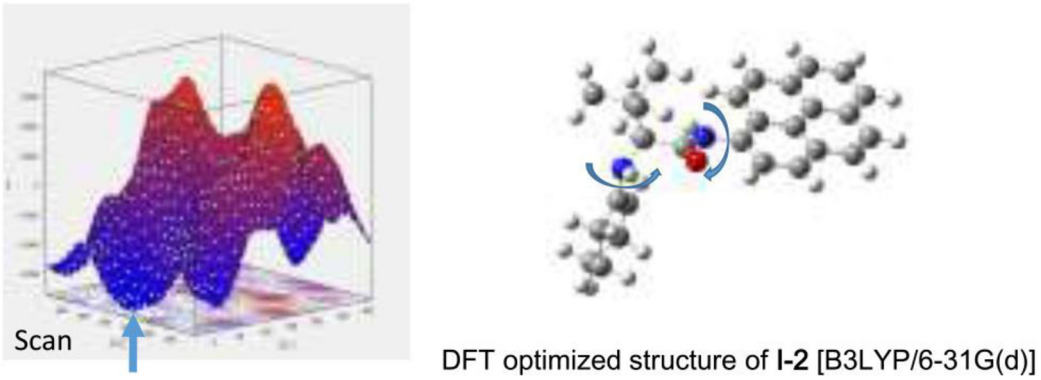


Figure 3. A scan of total energies of the intermediate (**I**) generated by varying two torsion angles (dihedral scans represented with u-shaped arrows, as shown in the right structure). The arrow at the bottom represents the global energy minimum conformer (in the left figure). Reprinted with permission from Ref. [70]. Copyright 2018, Elsevier.

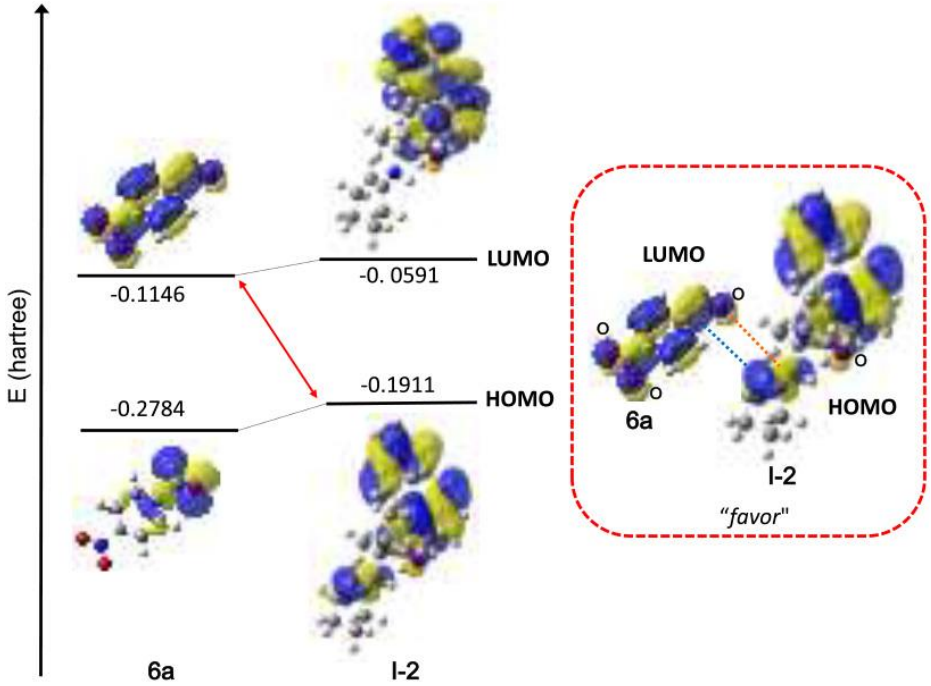


Figure 4. Frontier orbitals of **8** (**6a** in the figure represents **8** in our scheme) and **I-2** obtained by DFT calculations at the B3LYP/6-31G(d) level. Reprinted with permission from Ref. [70]. Copyright 2018, Elsevier.

Kaori Ishimaru et al. reported [71] the asymmetric aldol reaction of ketones with aromatic aldehydes using simple amino amides as organocatalysts based on electrostatic repulsion between oxygen in the amide and aromatic fluorine of the catalyst, along with the hydrogen-bonding interactions between the hydrogen of amide nitrogen and the fluorine of the aromatic group, to control stereoselectivity (Figure 5) [71]. The authors synthesized several amino amides (**11a**-**g**) and tested their efficacy as simple chiral agents in the asymmetric aldol reaction of various cyclic ketones (**12**) with substituted aromatic aldehydes (**13**) and isatins (Scheme 9). Among all screened catalysts, **11a**, which can generate hydrogen bonding and electrostatic repulsions, provided the highest yield (up to 99% yield) and selectivity (up to 99% *ee* and 1:99 = *syn*:*anti*).

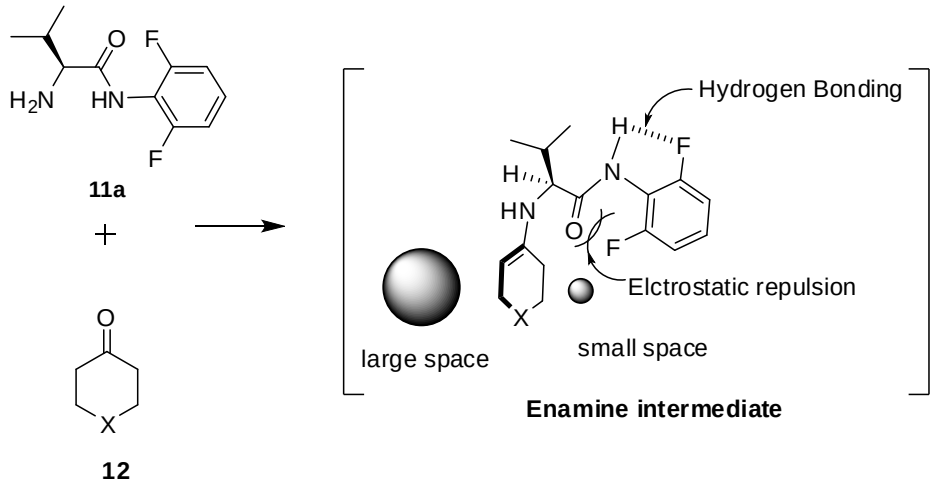
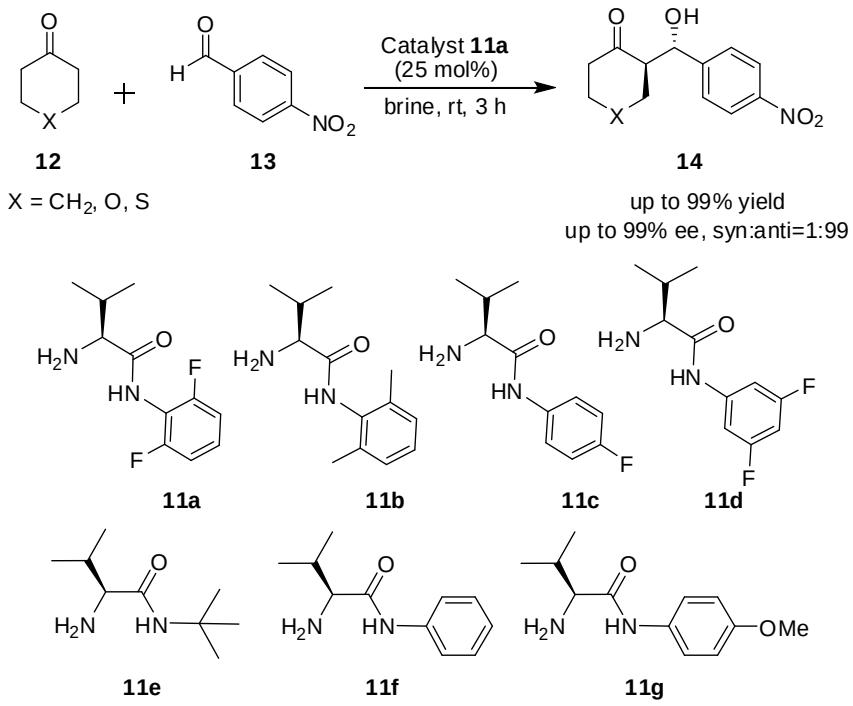


Figure 5. Concept of amino amide catalyst for asymmetric aldol reaction.



Scheme 9. Asymmetric aldol reaction using simple amino amides as chiral agents.

Using computational analysis, the authors detailed the mechanism, highlighting the importance of the best catalyst structure (**11a**) to provide high selectivity through hydrogen bonding and electrostatic repulsions when compared to other catalysts (Figure 6). The authors also used DFT calculations to study the transition-state structures in order to justify the *anti*-aldol product (Figure 7).

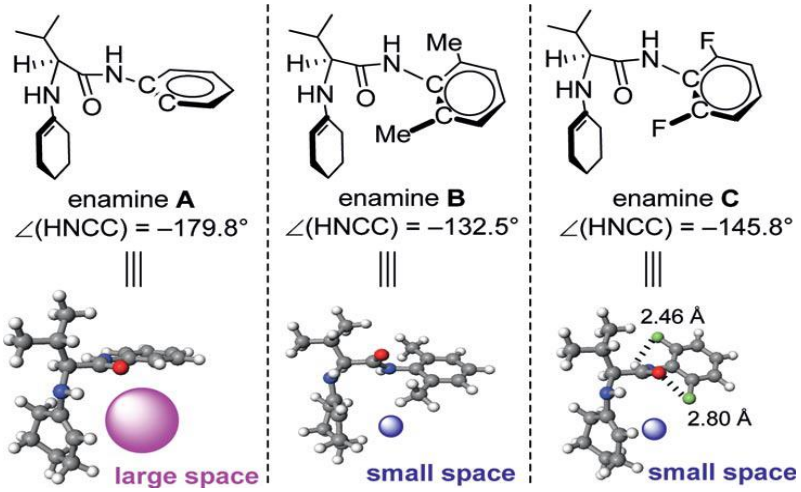


Figure 6. Enamine structures calculated at the B3LYP/6-31G(d,p) level.

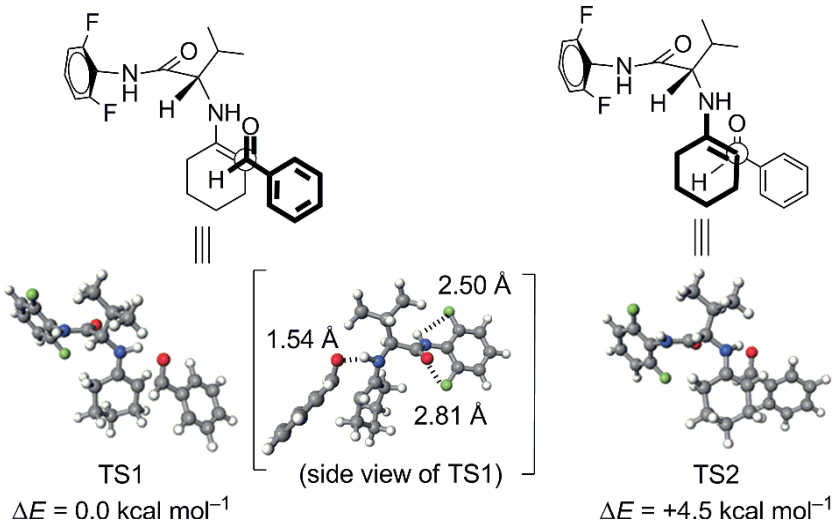
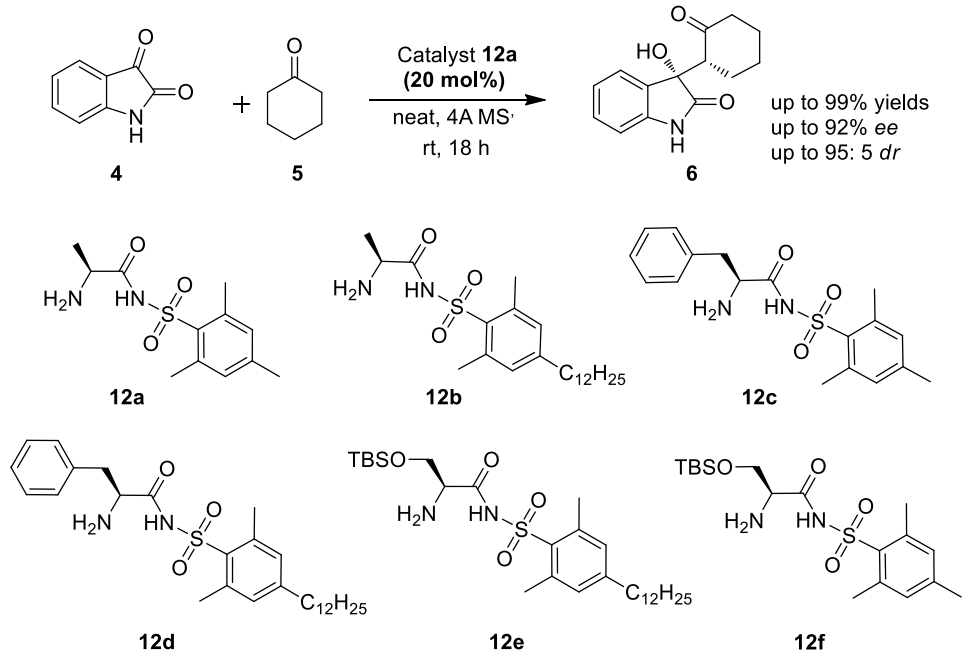


Figure 7. Calculated transition-state models for the asymmetric aldol reaction catalyzed by **11a**.

Hua Yang and colleagues [72] later showed that the α-amino acid sulphonamides (**12a**–**f**) may be employed as standalone bifunctional organocatalysts in asymmetric aldol processes without being linked to additional chiral moieties. They successfully catalyzed the asymmetric aldol reaction between isatin **4** and cyclohexanone **5** under neat conditions at room temperature by synthesizing a series of primary α-amino-acid-derived sulfonamides (**12a**–**f**) via direct coupling of Cbz-protected amino acids with sulphonamides, followed by deprotection.

They performed this reaction in various solvents and with various additives but discovered that molecular sieves, as privileged additives, played a critical role in achieving high enantioselectivity (up to 92% *ee*) and high diastereoselectivity (up to 95:5 *dr*) under neat reaction conditions with excellent yields (up to 99%) (Scheme 10). They also tested the practicality and reliability of their technique by scaling it up to 2 mmol; they discovered the same selectivities with good to exceptional yields utilizing their best catalysts (**12a**). Based on the experimental data and the influence of molecular sieves, they postulated a feasible reaction path in which hydrogen bonding between the N-H of sulphonamide and isatin would trigger an enamine re-face attack on the carbonyl group of isatin (**4**) (Figure 8).



Scheme 10. Asymmetric aldol reaction catalyzed by amino acid sulphonamides.

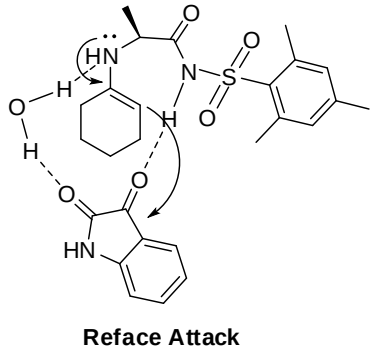
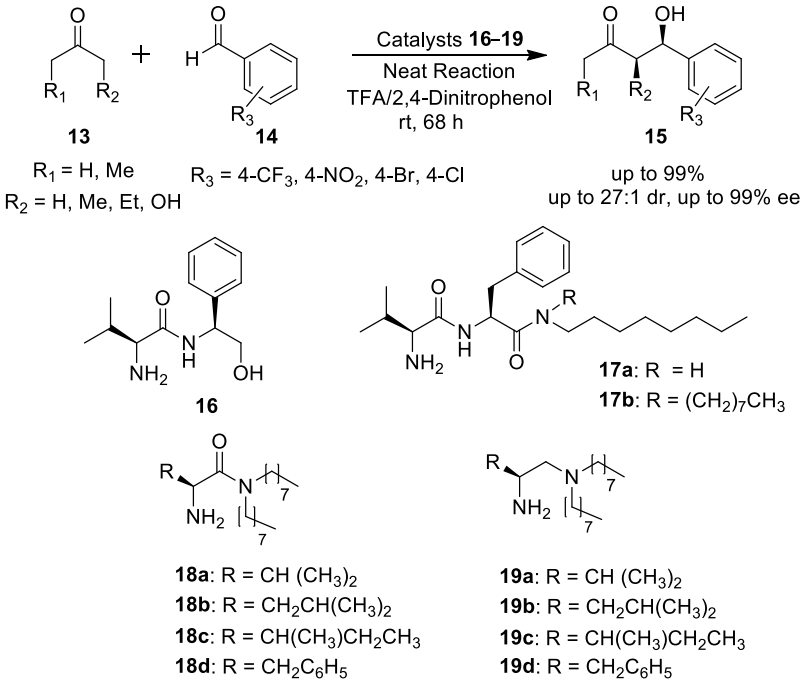


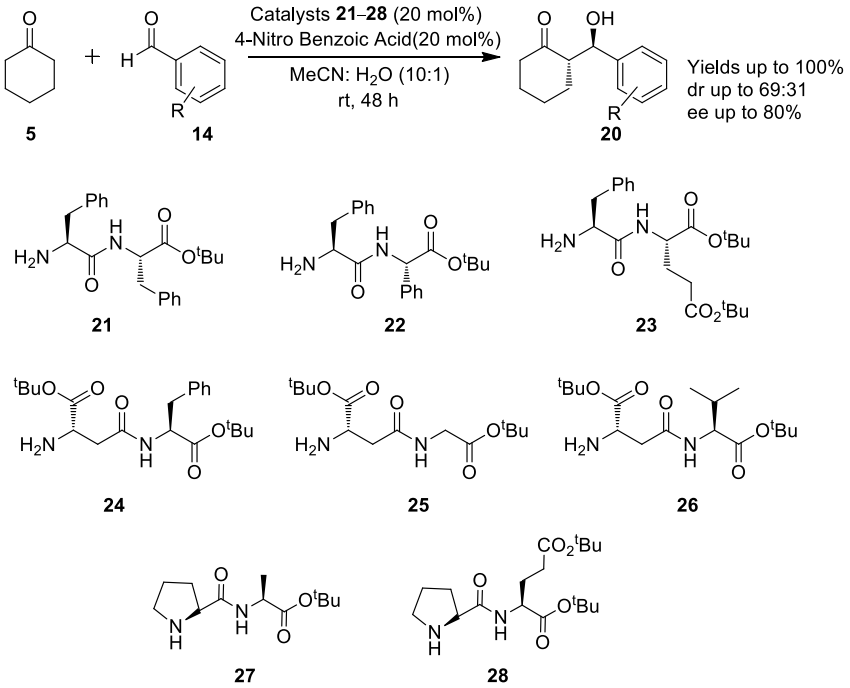
Figure 8. Proposed reaction mode of aldol reaction.

Bert F. Sels et al. [73] pioneered the *syn*-asymmetric aldol reaction of linear ketones with aromatic aldehydes at ambient temperature catalyzed by various amino acids, amino amides (**16**, **17**, and **18**) and diamines (**19**). (Scheme 11) [73]. The authors tested this reaction with numerous acids as additives, including TFA, CCl_3COOH, m-NO_2 bzac, $H_3PW_{12}O_{40}$, p-TSA, DNP, PhCOOH, TFA/AcOH, TFA/m-NO_2 bzac, and TFA/DNP. They used trifluoroacetic acid (TFA) as Bronsted acid and 2,4-dinitrophenol (DNP) as cocatalyst and successfully used the simple amino amides (**16**, **17**, and **18**) as bifunctional catalysts for this reaction. However, the yields and selectivity were insufficient. On the other hand, diamine catalysts (**19**) provided very high yields and outstanding selectivity for this syn-asymmetric aldol process.

Christoforos G. Kokotos et al. [74] then examined the efficacy of amino-amide-type catalysts (**21** to **26**) and prolinamide-type catalysts (**27** and **28**) in direct aldol condensation between several aromatic aldehydes and cyclic or acyclic ketones in acetonitrile and a water medium with 4-nitro benzoic acid as the cocatalyst (Scheme 12) [74]. The *anti*-aldol product was obtained with excellent yields (up to 100%) but with low to moderate diastereoselectivity (up to 69:31 *dr*) and enantioselectivity (up to 80% *ee*). However, they achieved the highest yields (up to 100%) and selectivity (98:2 *dr* and 99% *ee*) in this *anti*-aldol reaction at ambient temperature using a wet acetonitrile medium with 4-NBA as an additive.



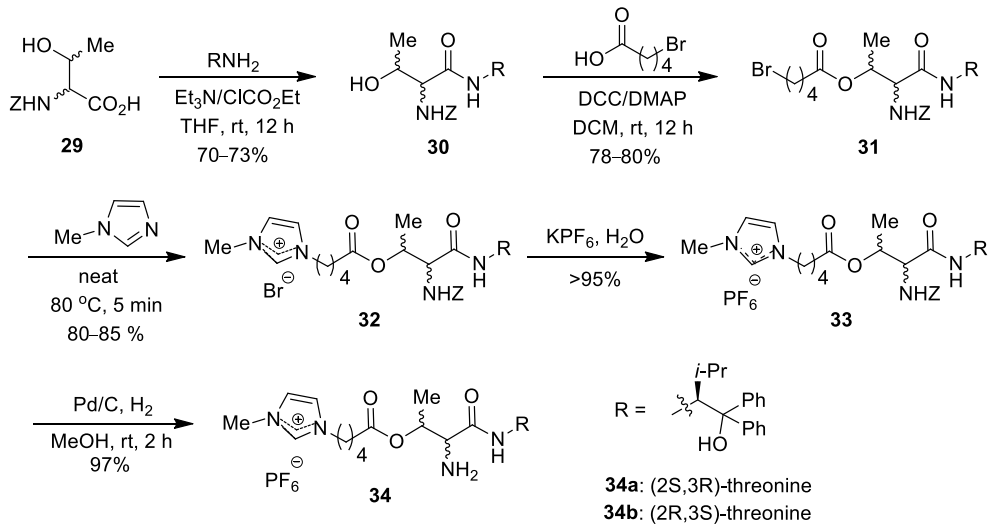
Scheme 11. Asymmetric aldol reaction of linear ketones with aromatic aldehydes catalyzed amino amides.



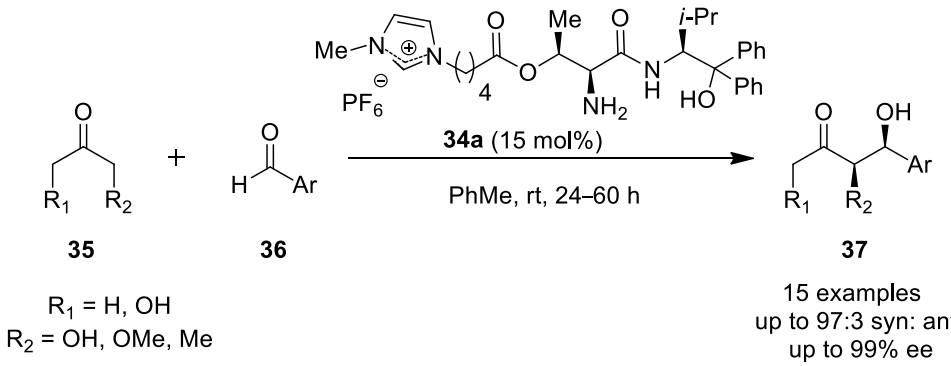
Scheme 12. Asymmetric aldol reaction catalyzed by amino amides.

In general, the predominant reaction products in aldol reaction have *anti* configuration. However, in extremely rare cases, *syn*-aldol products have been reported. Sergei G. Zlotin et al. [75] designed and synthesized the first chiral ionic liquid containing primary α-amino amides in 2011 (Scheme 13) and efficiently used these as self-determining organocatalysts for the aldol reaction of ketones with secondary carbon atoms at the α position with respect to the carbonyl group and aromatic aldehydes, yielding the corresponding *syn*-aldol products in high yields (up to 99%) (Scheme 14). These ionic liquid chiral primary α-amino amide catalysts (**34a–b**) were created by the authors using commercially available N-Cbz-protected threonine amino acids. Scheme 13 describes the entire synthesis operation.

Among these two created organocatalysts, (2S,3R)-threonine (**34a**) produced the appropriate *syn*-aldol products with higher selectivity than catalyst **34b** (Scheme 14). The authors also proved the viability of recycling the catalyst for this reaction, discovering that after three cycles, the catalyst yielded the *syn*-aldol products with no loss of selectivity or yield, although the reaction duration was increased to seven days from one day in the first cycle. The yield was suddenly reduced to 20% in the fourth cycle.

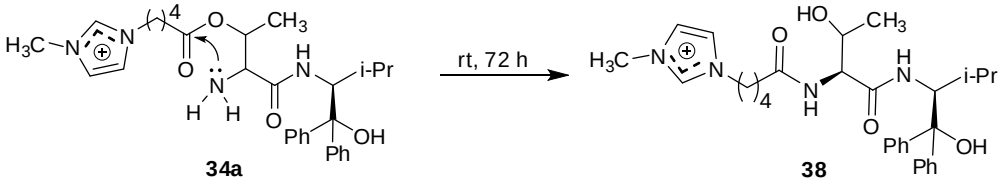


Scheme 13. Synthesis of (S) or (R)-threonine-derived catalysts (**34a** and **34b**) modified with ionic groups.



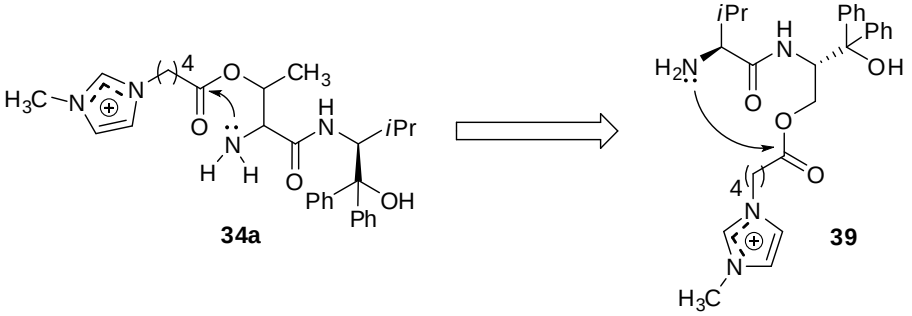
Scheme 14. **34a** catalyzed asymmetric syn-aldol reactions between compounds **35** and **36**.

The authors then began an inquiry to determine the cause of the catalyst **34a**'s unexpected deactivation after three cycles. In 2017, they discovered [76] that after 72 h, catalyst **34a** was transformed into a dipeptide compound (**38**) by the O-N migration of the carbonyl group via a five-membered transition state, as validated by the ^{1}H-^{13}C HMBC and HSQC spectral data of compound **38** (Scheme 15). As a result, the catalyst abruptly deactivated after 72 h [76].



Scheme 15. Transformation of **34a** to **38** according to the ^{1}H–^{13}C HMBC and HSQC spectral data.

The authors hypothesized that the simple displacement of the acyl spacer group from the threonine unit of catalyst **34a** to the distal amido-alcohol fragment might significantly slow the parasitic O–N migration rate (Scheme 16).



Scheme 16. Hypothesis of authors to prevent O-N migration.

To test this hypothesis, they synthesized compound **39** and calculated the distances between the primary amine **N-4** atom and the ester carbonyl **C-5** atoms in the minimum-energy conformations of the five-membered transition state of compound **34a** and the eight-membered transition state of compound **39** optimized at the PBE0–D3/cc-pVTZ level of theory with toluene solvation effects modelled with the solvation model based on density (SMD) (Figure 9) [76]. Quantum theory of atoms in molecules (QTAIM) analysis and subsequent application of Espinosa–Molins–Lecomte (EML) correlation for the strength of the noncovalent interaction revealed strong hydrogen bonds between the 1-H and **O-2** atoms (ca. 12.8 kcal mol-1), as well as between the amine **N-4** and **3-H** atoms (ca. 6.9 kcal mol-1), which is expected to additionally stabilize the open-chain conformation of **39** and prevent the intramolecular approach of the amine unit to the ester group required for the undesirable **O–N** migration.

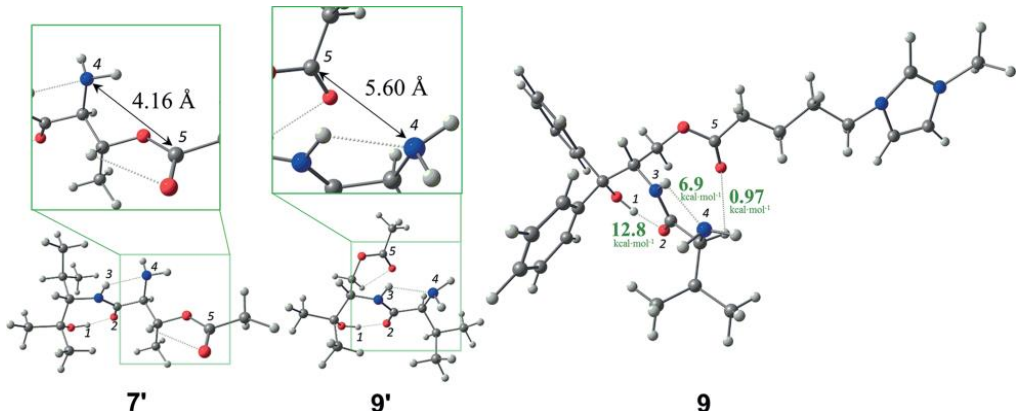
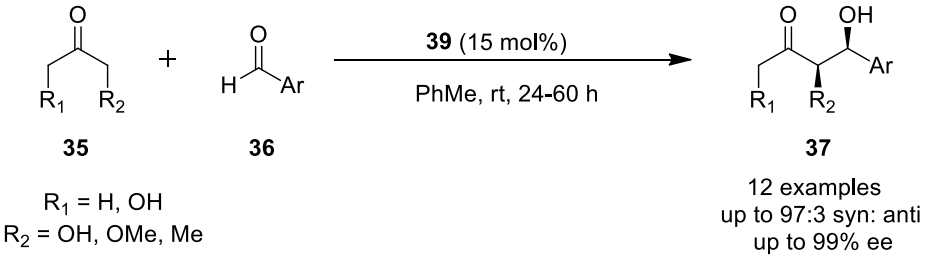


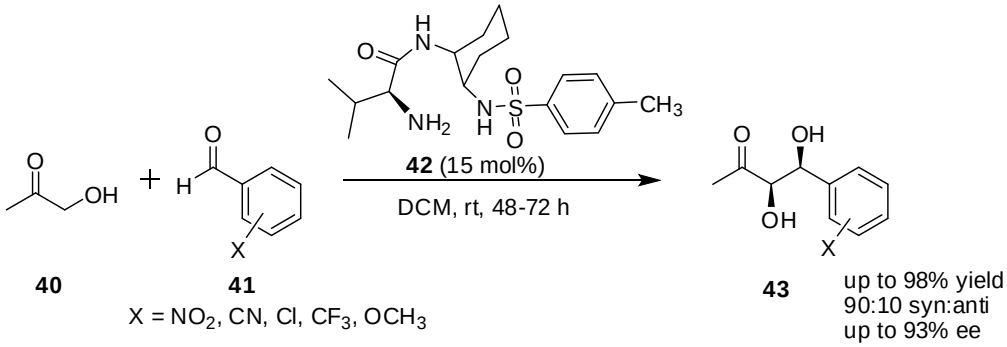
Figure 9. Minimum-energy conformers of model compounds of the five-membered transition state (7′) of **34a** and the eight-membered transition state (**9′**) of compound **39** (**9**) optimized at the RIJCOSX-PBE0–D3–gCP/def2-TZVP SMD and PBE0–D3/cc-pVTZ SMD energy level theory.

The authors investigated the catalytic capability of a newly synthesized ionic liquid-supported amino amide catalyst (**39**) in the presence of the above reaction conditions for the identical aldol reaction (Scheme 17). High yield and selectivity were found for the matching aldol product (up to 99%, *dr*; 97:3, 99% *ee*). The hypothesis that catalyst **39** has good catalytic for proficiency as many as seven cycles without affecting stereo induction was proven.



Scheme 17. Efficiency of catalyst **39** in aldol reaction.

Headly et al. [77] developed and synthesized a new series of cyclohexanediamine organocatalysts (**42**) with primary amine function as an enamine source and explored their catalytic effectiveness in the *syn*-aldol reaction of hydroxyacetone (**40**) with a range of substituted benzaldehydes (**41**). The associated *syn*-aldol compounds achieved high yields and high selectivity (up to 98%, *syn*/*anti*: 90/10, up to 93% *ee*) (Scheme 18).



Scheme 18. Syn-aldol reaction using a chiral primary amine organocatalyst.

Owing to the hydrogen link between the OH group of hydroxyl acetone and the acetic proton of enamine nitrogen, a stable Z-isomer (**44**) is preferred, yielding a *syn*-aldol product by interaction of this acetic proton with the oxygen of the carbonyl group of aldehyde (**45**). (Figure 10).

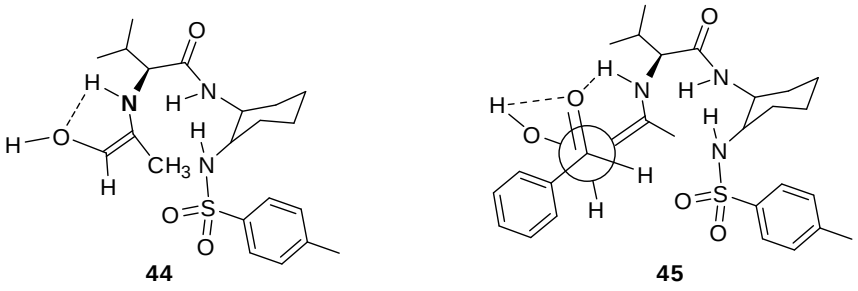
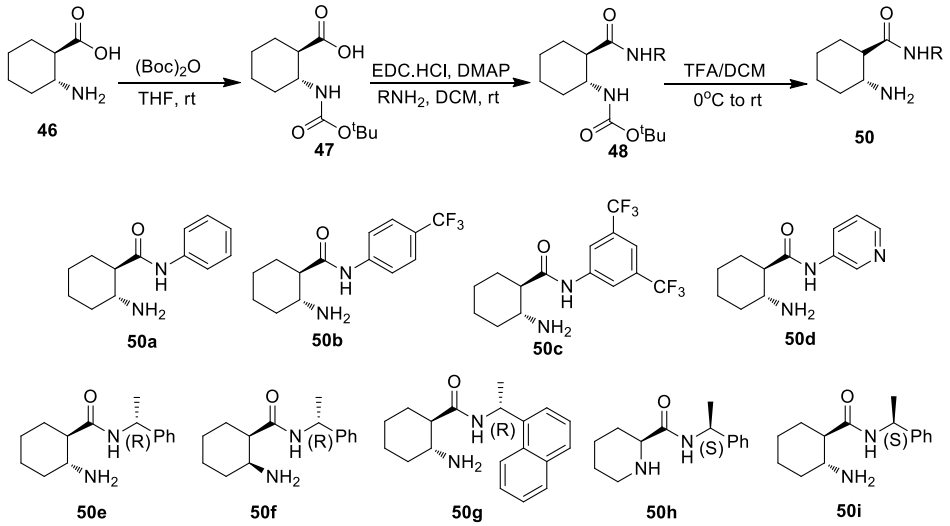


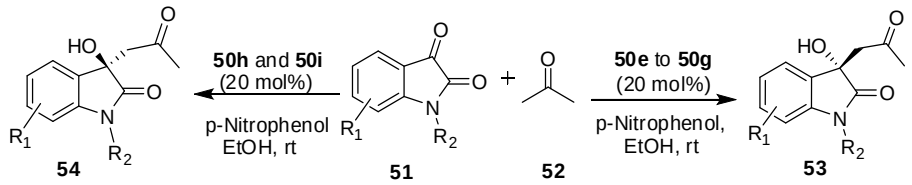
Figure 10. Stable conformers **44** and **45** through which a syn-aldol product was formed.

In 2019, Michael Kinsella et al. [78] described a direct asymmetric aldol reaction involving isatin and acetone (along with cyclic ketones) in the presence of chiral sources such as β-amino amides. The authors synthesized catalysts **50a–d** (Scheme 19) for the initial catalytic design and investigated their catalytic efficiency in the aldol process. Although the aldol adducts were produced in moderate to exceptional yield (up to 99%), enantioselectivity was evident in all cases. The authors predicted that the addition of a second chiral center would increase chiral selectivity in aldol adducts. They created new chiral β-amino amides (**50e** to **50i**) and tested them in the aldol reaction. Comparable aldol adducts were produced with high yields (up to 99%) and diastereoselectivity (up to 99% *dr*) but with low enantioselectivity (up to 52% *ee*). According to the authors' predictions, the newly introduced chiral center plays an important role in acquiring chirality in aldol products, as evidenced by changing the chiral center in catalysts **50h** and **50i**, which produced opposite

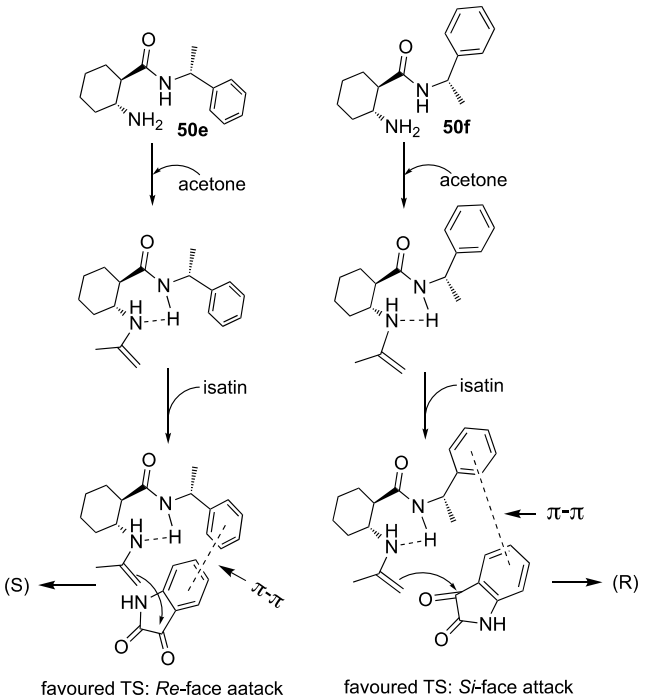
enantiomers in comparison to **50e** to **50g** as a result of the opposite configuration of the phenyl ethyl group attached to the amide moiety (Scheme 20). The hypothesized process shown in Scheme 21 demonstrates the significance of an additional chiral center in inducing chirality in aldol products. The steric component of the phenyl group and the interaction between the phenyl group and isatin **51** determines isatin's approach to enamine.



Scheme 19. Design and synthesis of various amino amide organocatalysts.



Scheme 20. Aldol reaction using β-amino amides as catalysts.

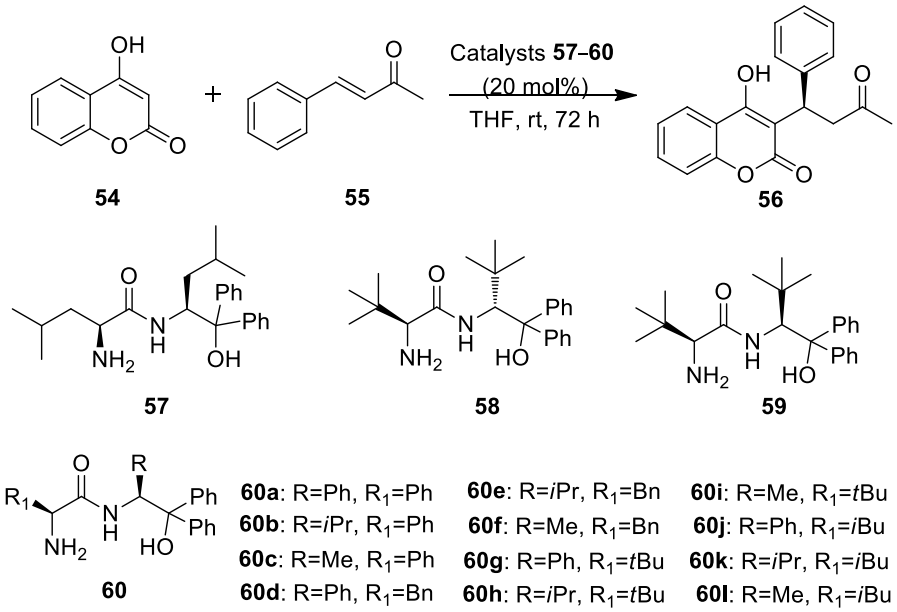


Scheme 21. Proposed mechanism of aldol reaction using β-amino amides as organocatalysts.

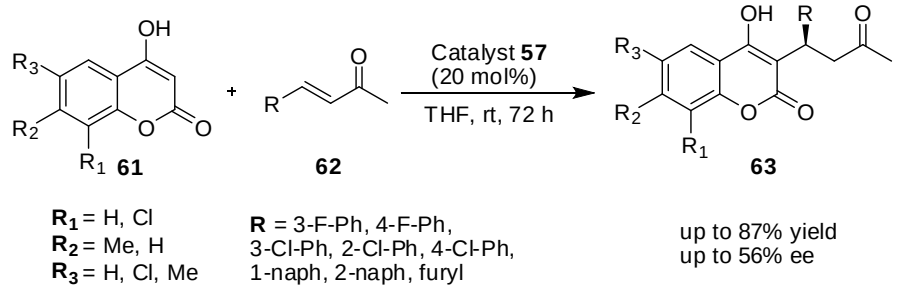
2.2. Asymmetric Michael Reaction

The Michael addition reaction is an example of one of the most influential methods for the creation of carbon–carbon bonds with full atom economy in organic synthesis [79–82]. The asymmetric Michael reaction is one of the most versatile, direct, and appealing approaches to organic synthesis [83–85]. The Michael addition of 4-hydroxycoumarin to benzylidenacetone in the presence of chiral scaffolds as catalysts is a simple way to produce enantiomerically enriched warfarin, which is an effective and relatively safe medication for thrombosis and embolism prevention [86–88]. Owing to warfarin's intriguing biological action, our research has focused on the synthesis of its chiral variants. We examined the possibility of α-amino amides as chiral templates (**57** to **60**) in the synthesis of chiral warfarin (**56**) from 4-hydroxycoumarin (**54**) and benzylidenacetone (**55**) in 2015 [89].

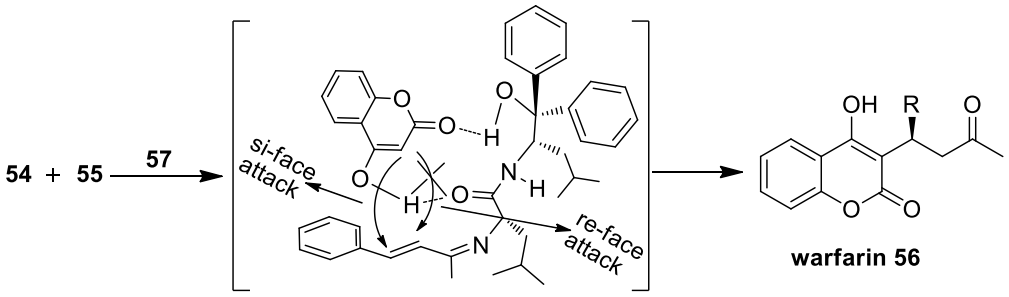
The α-amino amide alcohol catalysts **57** to **60** were made from the appropriate amino acids and α-amino alcohols and employed in the direct Michael addition of 4-hydroxycoumarin (**54**) to benzylidenacetone (**55**) to generate chiral warfarin (**56**) with up to 92% yield and up to 52% *ee* (Scheme 22). We also produced a variety of warfarin derivatives (**63**) from various 4-hydroxycoumarins (**61**) and unsaturated ketones (**62**) (Scheme 23) with good yields and moderate enantioselectivity under optimal reaction conditions utilizing our best catalysts (**57**). The proposed transition state model shown in Scheme 24 demonstrates that *si*-face attack is more advantageous than re-face attack for harvesting chiral warfarin.



Scheme 22. Asymmetric synthesis of warfarin using amino amides as chiral templates.

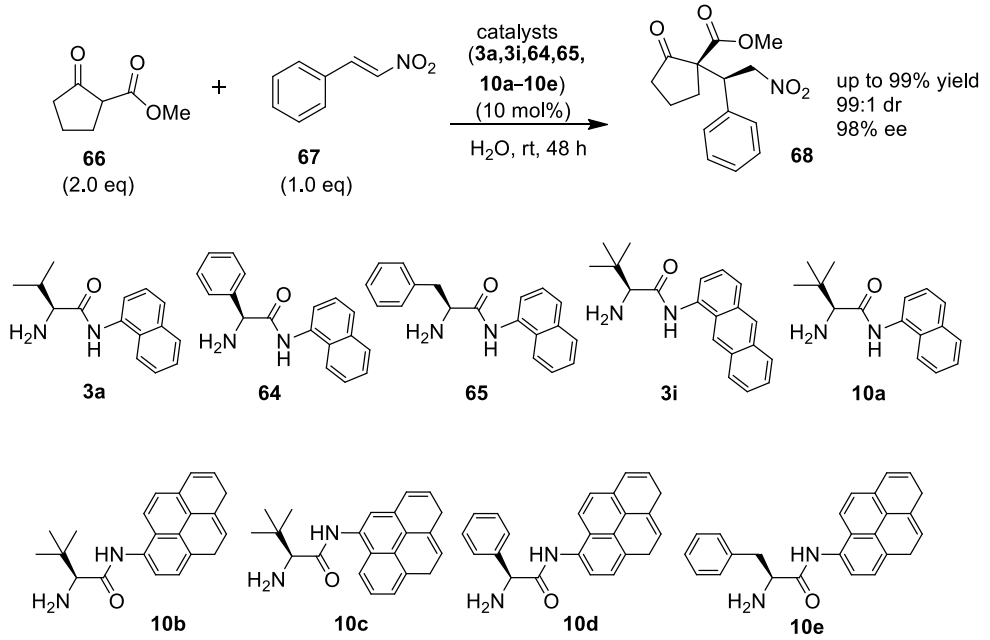


Scheme 23. Asymmetric synthesis of warfarin derivatives.



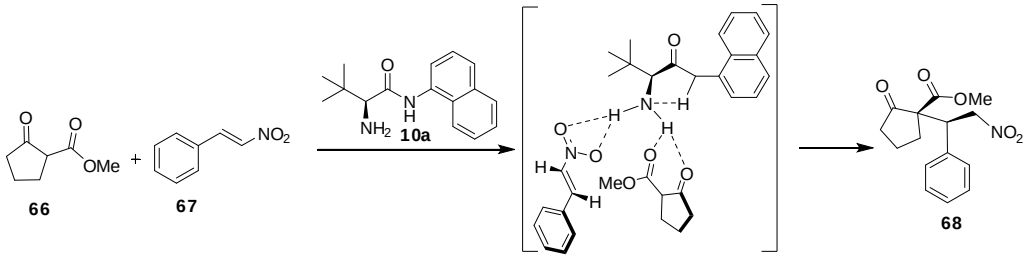
Scheme 24. Proposed transition-state model of Michael addition.

Recently, we investigated the catalytic proficiency of α-amino amide catalysts (**3a**, **3i**, **10a** to **10e**, **64**, and **65**) with primary amine groups for enamine formation and hydrogen bond formation. We also investigated the amide group as a hydrogen bonding site in the Michael addition reaction of β-keto esters (**66**) with trans-nitro olefins (**67**) in aqueous medium at room temperature [90]. Our finest catalyst for this transformation (**10a**) (5 mol%) offered a Michael adduct with outstanding selectivity and yield (up to 99%, *dr*; 99:1, *ee* 98%) under environmentally acceptable reaction circumstances (Scheme 25). To improve selectivity, the bulky flexible polycyclic aromatic ring on the nitrogen atom of the amide group in the catalyst may be successfully sheltered by a steric component on the one enantiotopic face.



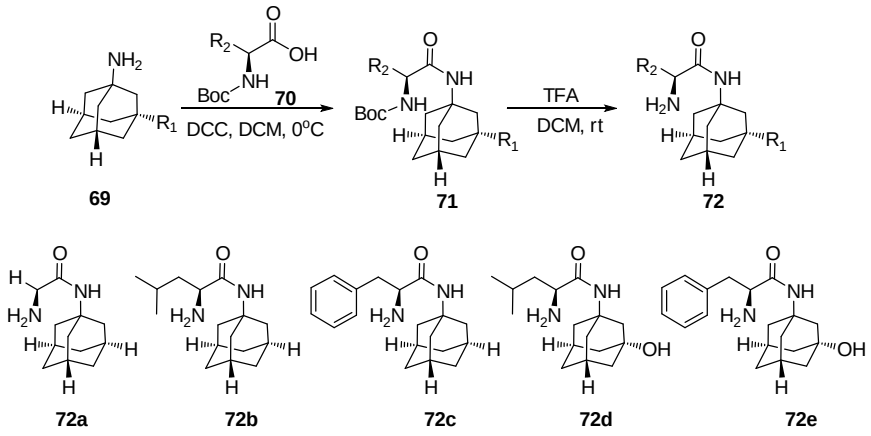
Scheme 25. Michael addition in the presence of amino amides as chiral templates.

Scheme 26 depicts the hypothesized reaction transition state. The creation of enamine species was not detected in this reaction based on the calculation findings of the scan total energy of catalyst **10a** and the electrostatic potential maps of **10a**, as well as the calculation of the energies and coefficients of frontier orbitals of reactants **66** and **67** [90]. This finding suggests that amino amide **10a** may operate as a basic catalyst via hydrogen bonding between oxygen in the nitro group and hydrogen in the primary amine, as well as between oxygen in the keto ester and hydrogens in the primary amine.

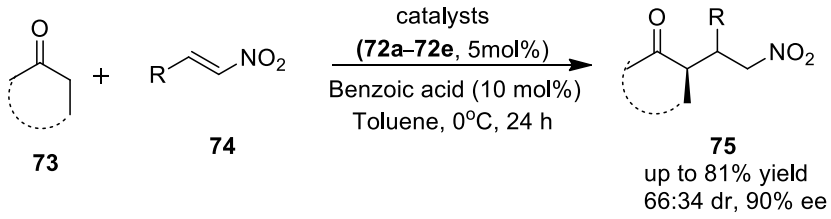


Scheme 26. Proposed reaction mechanism of Michael addition using amino amides as chiral agents.

Kun Wei et al. [91] developed and synthesized adamantyl-based prolinamides and primary amino amides in 2015 (Scheme 27). The catalytic activity of these synthesized α-amino amides for Michael addition of aldehydes and ketones to nitroalkenes was investigated by the authors. After testing numerous acids and bases as additives in various solvents, they discovered that toluene is the best solvent and benzoic acid is the leading additive for this Michael addition. The prolinamide adamantoyl catalysts were superior in producing these Michael adducts. In addition, the primary α-amino amide adamantoyl as chiral catalysts also produced the corresponding products in moderate to good yields and selectivities under optimized reaction conditions (Scheme 28).



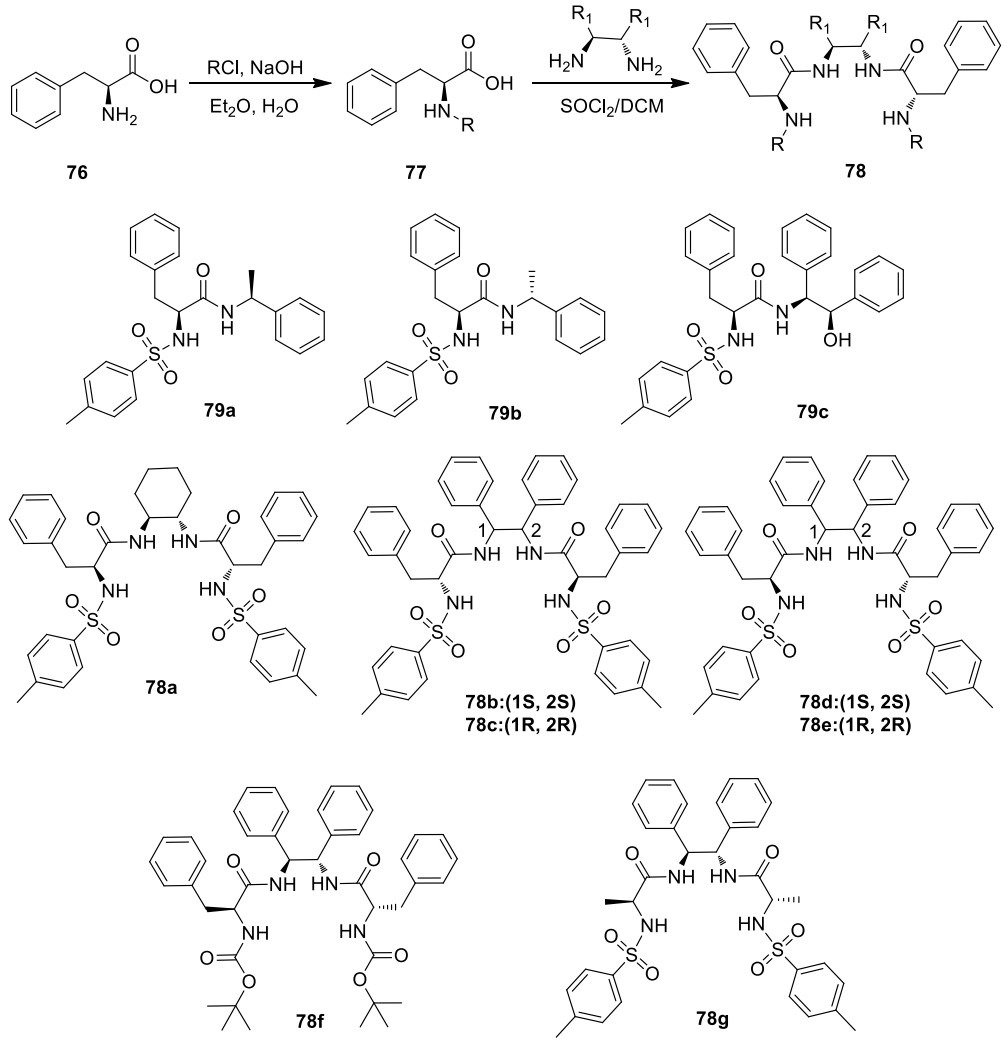
Scheme 27. Synthesis of adamantoyl amino amides.



Scheme 28. Asymmetric Michael reaction in the presence of adamantoyl amino amides as organic catalysts.

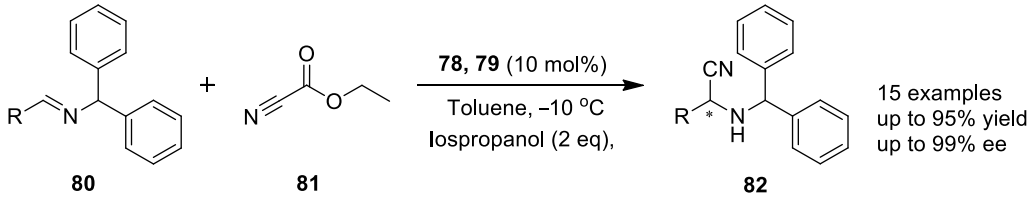
2.3. Asymmetric Strecker Reaction

The asymmetric Strecker reaction is one of the simplest and most cost-effective multicomponent reactions, involving the hydrocyanation of imines to yield α-amino nitrile, which is then hydrolyzed to yield natural and un-natural α-amino acids [92,93]. Asymmetric amino acids are crucial protocols in many biological active scaffolds. Many asymmetric Strecker procedures mediated by metal [94–96] and free of metal [97] have been reported and recorded. In 2012, N.H. Khan et al. [98] developed and synthesized a series of C1- and C2-symmetric amino amide organocatalysts with variable steric characteristics and one to four chiral centers from L-phenyl alanine in two simple stages (Scheme 29).



Scheme 29. Synthesis of C1- and C2-symmetric amino amide organocatalysts.

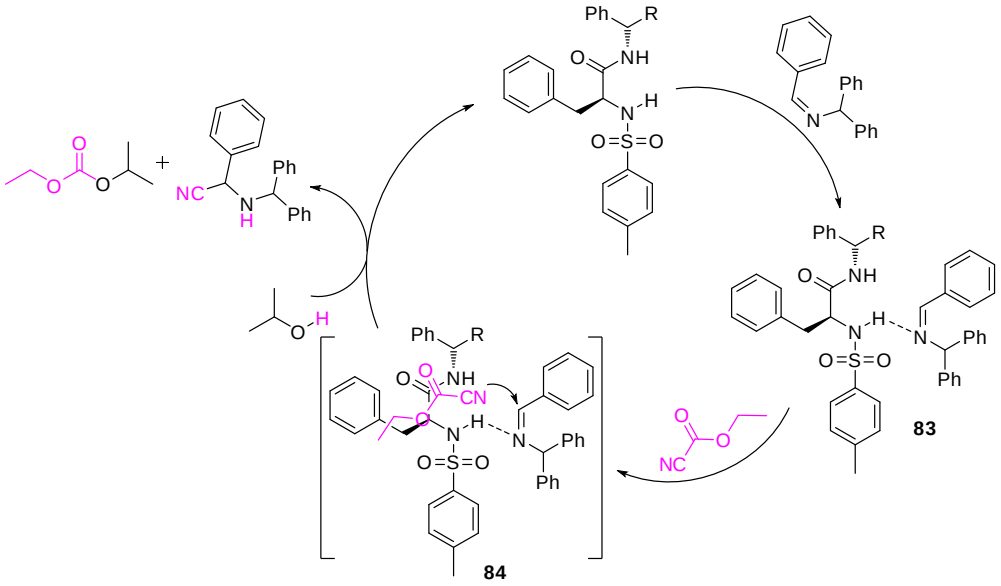
The authors investigated these C1- and C2-symmetric amino amide organocatalysts (**79** and **78**) in toluene for the enantioselective Strecker reaction of N-benzhydrylimine (**80**) with ethyl cyanoformate (**81**) as a cyanide source. All tested organocatalysts showed catalytic activity in the production of enantioselective α-amino nitriles with moderate to high yields and selectivity (Scheme 30), confirming that the C2-symmetric catalyst (**78d**) (10 mol%) optimally furnished the Strecker product, i.e., α-aminonitriles (**82**) in toluene as a solvent and *i*-PrOH as an additive and proton source at −10 °C in high yield (95%) with excellent chiral induction (up to 99% *ee*) (Scheme 30).



Scheme 30. Enantioselective Strecker reaction of N-benzhydrylimine (**80**) with ethyl cyanoformate (**81**) in the presence of organocatalysts **78** and **79**.

Scheme 31 shows the reaction path of this transition. In the first stage, the imine nitrogen of N-benzhydrylimine bonded with the more acidic proton of the catalyst's sulphonamide origin. To obtain the end product, the CN group was transferred from ethyl

cyanoformate, followed by the transfer of an acidic proton from the additive, *i*-PrOH. The recyclability of best catalyst (**78d**) was also investigated, and it was discovered that it could provide the product for up to three cycles without losing yield or selectivity.



Scheme 31. Reaction course of Strecker reaction using catalyst **78d**.

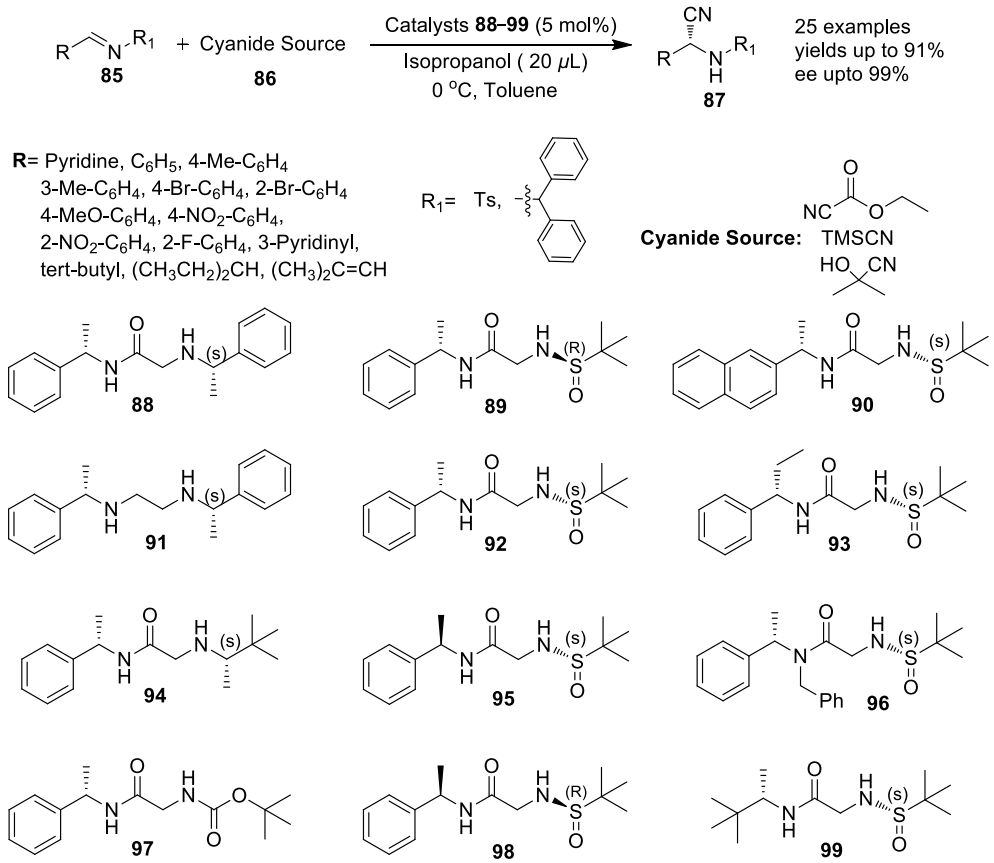
Later, the same Strecker reaction was reported [99] with a variety of N-benzhydryl- and N-tosyl-substituted imines (**85**) in the presence of simple N-sulfonamide amino amide chiral catalysts (**88–99**) using various cyanide sources, such as ethyl cyanoformate, TMSCN, and acetone cyanohydrin (**86**), and *i*-PrOH as additive and proton source at 0 °C (Scheme 32). In the case of both N-benzhydryl- and N-tosyl-substituted imines, they achieved the corresponding α-amino nitriles (**87**) in 24 h at 0 °C with high yield (up to 91%) and outstanding enantioselectivity (up to 99% *ee* of product) (Scheme 32). Among the evaluated chiral sources, catalyst **92** produced the best results under optimum reaction circumstances (yields up to 91%, up to 99% *ee*) (Scheme 32). The authors thoroughly investigated the optimum reaction conditions in order to achieve high yield and selectivity. They discovered that the addition sequence of reactants, including the cyanide source, is critical to obtaining optimal outcomes. The addition of a cyanide source to the best catalyst (**92**), followed by the addition of an imine, resulted in a significant shift in enantioselectivity for all three cyanide sources.

These findings show that the cyanide sources interacted with catalyst **92**, which was validated by ^{1}H-NMR spectra. The authors also presented a stereo selection model for the hydrocyanation of imines based on their research, as illustrated in Figure 11.

2.4. Enantioselective Allylation of Aldehydes

In 2013, Sayed H.R. Abdi et al. [100] reported the metal-free asymmetric synthesis of homoallyl alcohol from the well-known allylation process of carbonyl compounds. These are crucial building blocks for the synthesis of physiologically active chemicals. In outstanding yields, the authors developed and synthesized tosylated L-phenylalanine derivatives as effective catalysts, i.e., **100** to **110**, in a single step by amidation of tosylated L-phenylalanine/L-alanine/L-phenyl glycine. These new chiral amides (**100** to **110**) served as effective organocatalysts for the reaction of allyl-trichlorosilane **112** with aryl, hetero-aryl, and, α, β-unsaturated aldehydes (**111**) to generate the required homoallylic alcohols in good yield (up to 90%) and high enantioselectivity (up to 99%). (Scheme 33). They discovered that catalyst (**101**) had the best selectivity in the presence of diisopropylethylamine (DIPEA, 2.0 eq.) as an additive in CH_2Cl_2: THF (7:3) at 0 °C. According to the experimental data

and DFT calculations, para-substituted aromatic aldehydes as a substrate exhibited higher *ee* in the product than ortho/meta equivalents. Figure 12 depicts the reaction path.



Scheme 32. Strecker reaction of N-benzhydryl- and N-tosyl-substituted imines.

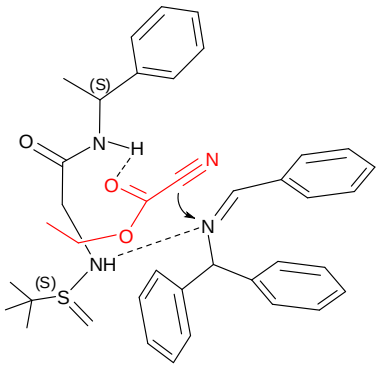
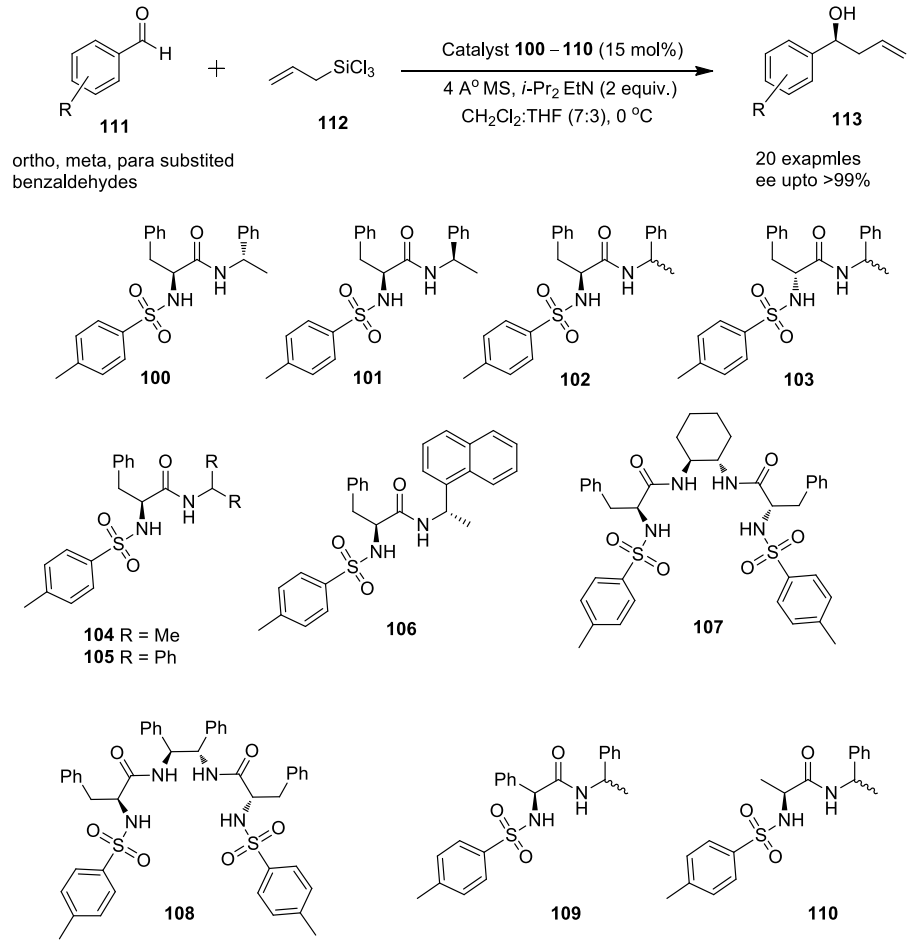


Figure 11. Proposed stereoselection model for the hydrocyanation of imines.



Scheme 33. Asymmetric allylation of aromatic aldehydes in the presence of tosylated amino amides as chiral organocatalysts.

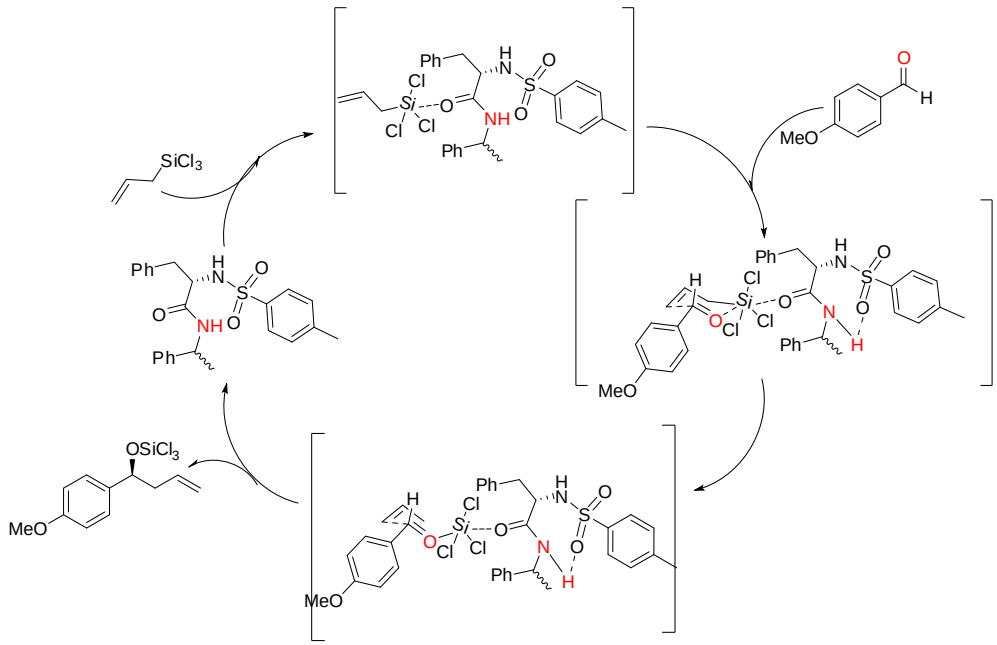
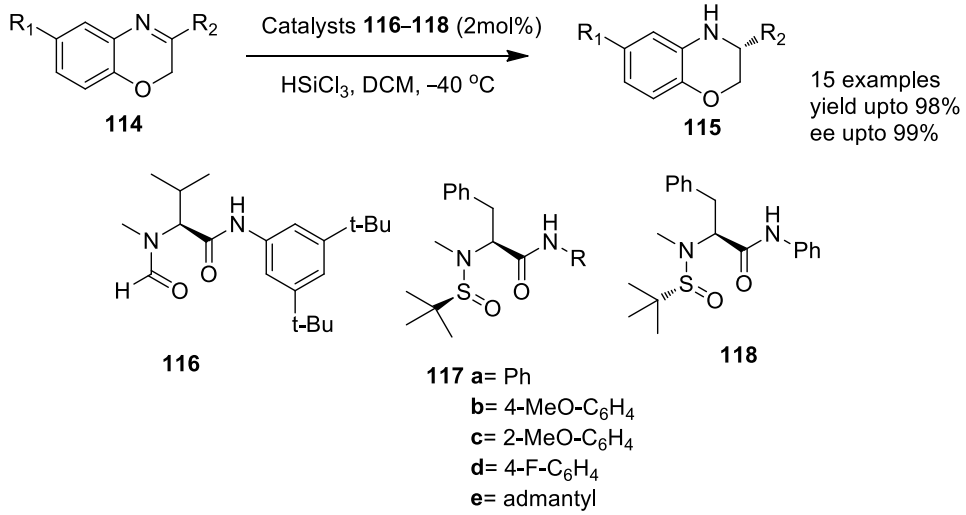


Figure 12. Reaction course for chiral allylation of aldehydes.

2.5. Hydrosilylation of 1,4-Benzooxazines

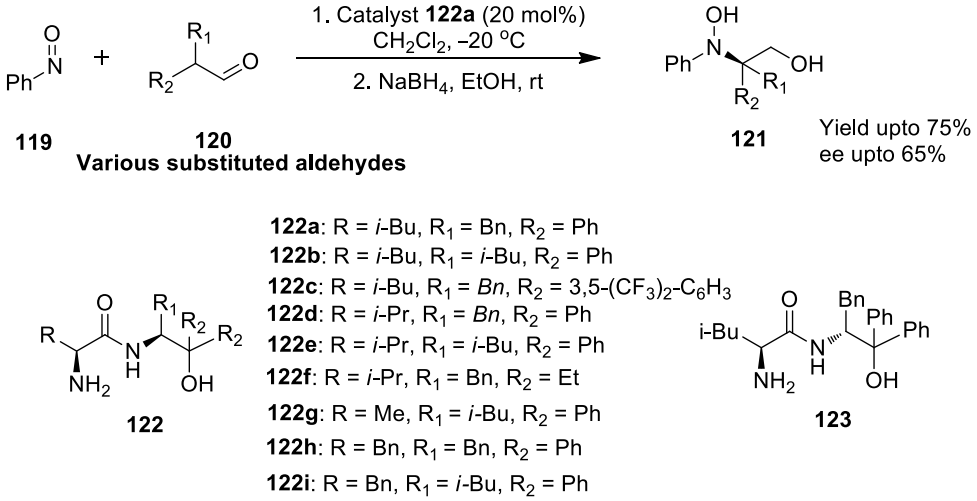
Chiral 3-substituted 3,4-dihydro-2H-1,4-benzooxazine is an important structural motif in chiral pharmaceuticals, as well as medically interesting natural chemicals, such as obscurinervidine, niblinine, and levofloxacin. The development of an organocatalyst to synthesize chiral 3-substituted 3,4-dihydro-2H-1,4-benzoxazine is significant and exceedingly valuable. Jian Sun et al. [101] developed the amino amide catalysts **116–118** as new Lewis base organocatalysts. **117** and **118** have stereogenic sulfur centers, along with stereogenic carbon. Th authors successfully employed them to synthesize 3-substituted 3,4-dihydro-2H-1,4-benzooxazines via an asymmetric procedure. Catalyst **117b** is exceedingly active, with 2 mol% of this catalyst forming the suitable chiral 3-aryl-3,4-dihydro-2H-1,4-benzooxazine products (**115**) via hydrosilylation with good to high yields (66–98%) and enantioselectivity (70–99% *ee*) (Scheme 34).



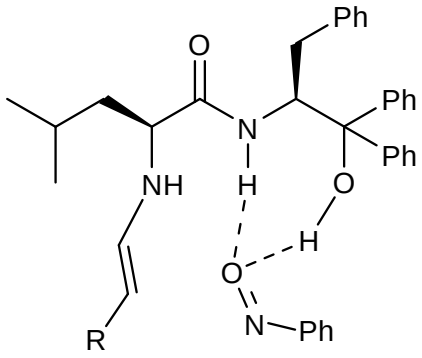
Scheme 34. Amino-amide-catalyzed hydrosilylation of 1,4-benzooxazines.

2.6. Asymmetric N-Specific Reaction of Nitrosobenzene with Aldehydes

Atom-specific reactions are both fascinating and important for the production of diverse products using a molecule with varied reactive atoms. Nitroso compounds are appealing because their N and O atoms are highly reactive toward nucleophiles, and they are widely used to construct structures containing nitrogen or oxygen. Yi-Feng Zhou et al. [102] successfully synthesized simple α-amino amide organocatalysts **122–123** with hydroxyl functional groups in 2011 and employed them in the enantioselective N-specific reaction of nitrosobenzene with unmodified aldehydes. The corresponding aldehyde hydroxyamination products (**121**) were produced increased yield and selectivity (Scheme 35). After screening multiple solvents at various temperatures, the best results were obtained using CH_2Cl_2 as a solvent at −20 °C in the presence of 20 mol% of the most efficient catalyst, i.e., **122a**. The reaction process is explained in Scheme 36. The presence of the base had no effect on enantioselectivity. Owing to the bulkier substituents of the organocatalyst and the two hydrogen bonds formed between two hydrogen atoms of amide and hydroxyl groups and the oxygen atom of nitrosobenze, the reaction is nitrogen-selective. Furthermore, the larger group of an aldehyde's carbon chain at the β-carbon can boost product enantioselectivity, whereas α-substituted aldehydes often achieve lower enantioselectivity.



Scheme 35. Amino-amide-catalyzed asymmetric N-specific reaction of nitrosobenzene.

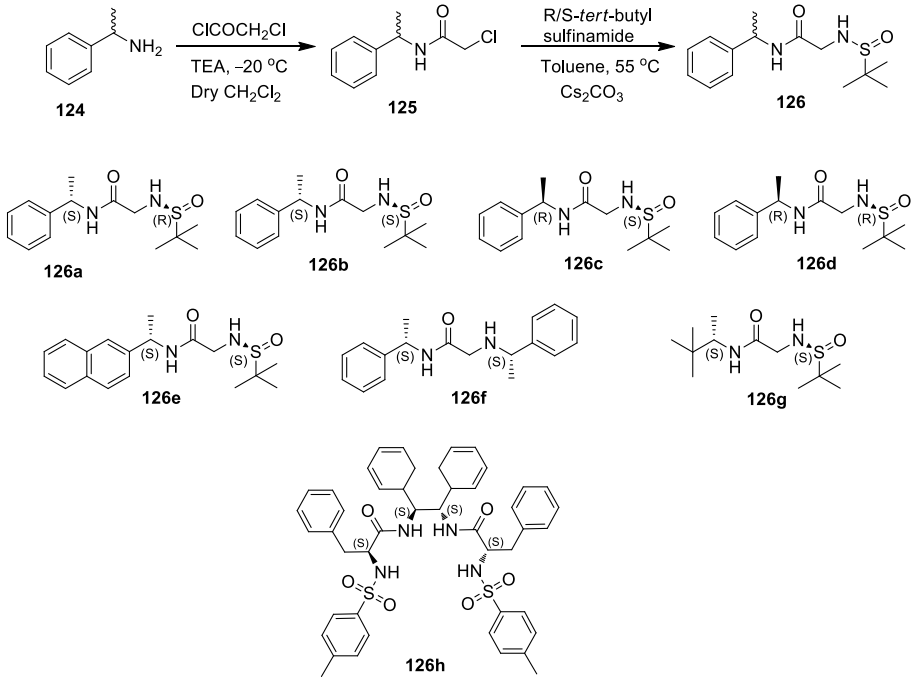


Scheme 36. Reaction process of asymmetric N-specific reaction of nitrosobenzene with aldehydes.

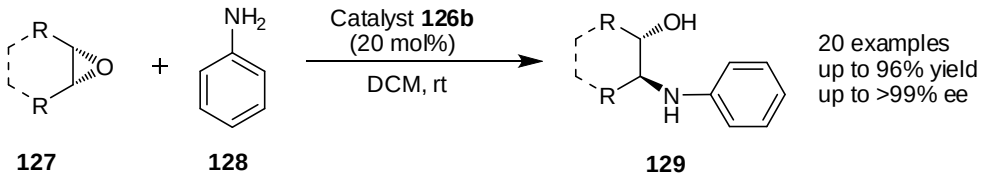
2.7. Opening of Epoxide

Kurshy et al. [103] designed and synthesized a simple chiral sulfinamide-based organocatalyst from commercially available starting materials and used it successfully for the asymmetric ring-opening (ARO) reaction of meso-epoxides with anilines. They created chiral promoters by protecting primary amines with chloroacetyl chloride and replacing the chlorine atom with sulfinamide groups (Scheme 37). The authors investigated the reaction conditions for the model reaction, such as catalyst loading and solvent choice. They concluded that 20 mol% of catalyst **126b** and dichloromethane as solvent at room temperature produced the corresponding product (**129**) with high yield (up to 96%) and excellent enantiomeric excess (up to >99% *ee*) (Scheme 38).

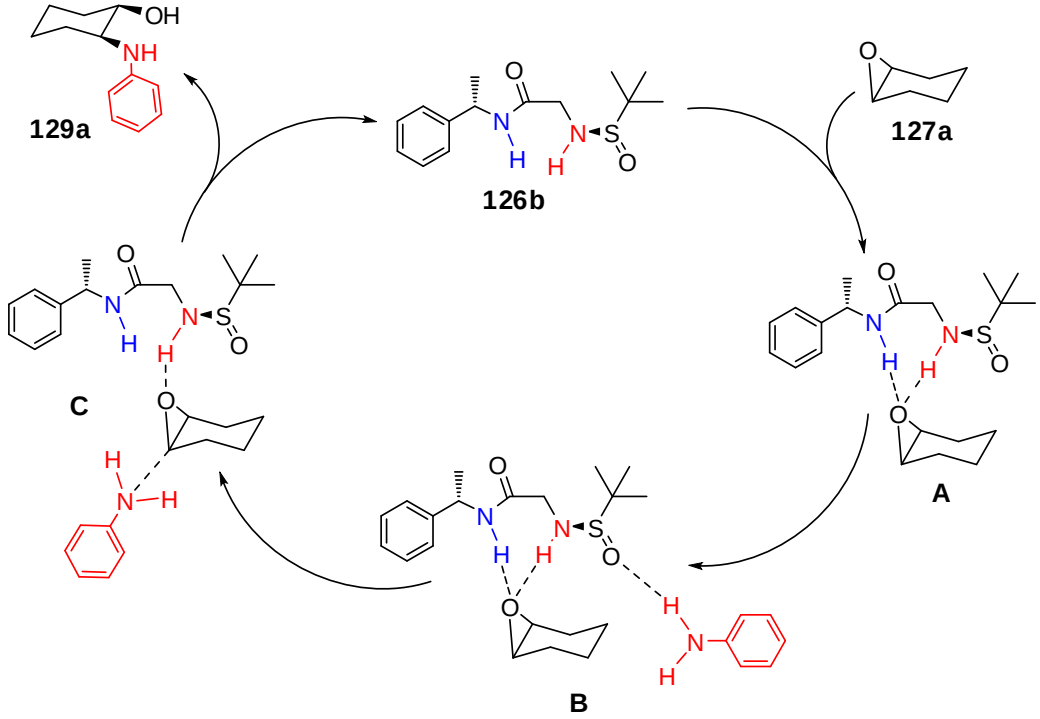
The experimental examination of ^{1}H and ^{13}C-NMR spectra led to the predicted reaction pathway depicted in Scheme 39. The interaction of the catalyst with the epoxide substrate was studied and confirmed with chemical shift values of N-H protons in ^{1}H-NMR at various stages of the reaction course via hydrogen bonds between N-H protons of the carbonyl, as well as sulfonyl moieties of the catalyst with the oxygen of the epoxide. This was supported by ^{13}C-NMR of the catalyst and NMR spectra of the epoxide.



Scheme 37. Synthesis of chiral sulfinamide organocatalysts **126a–126h**.



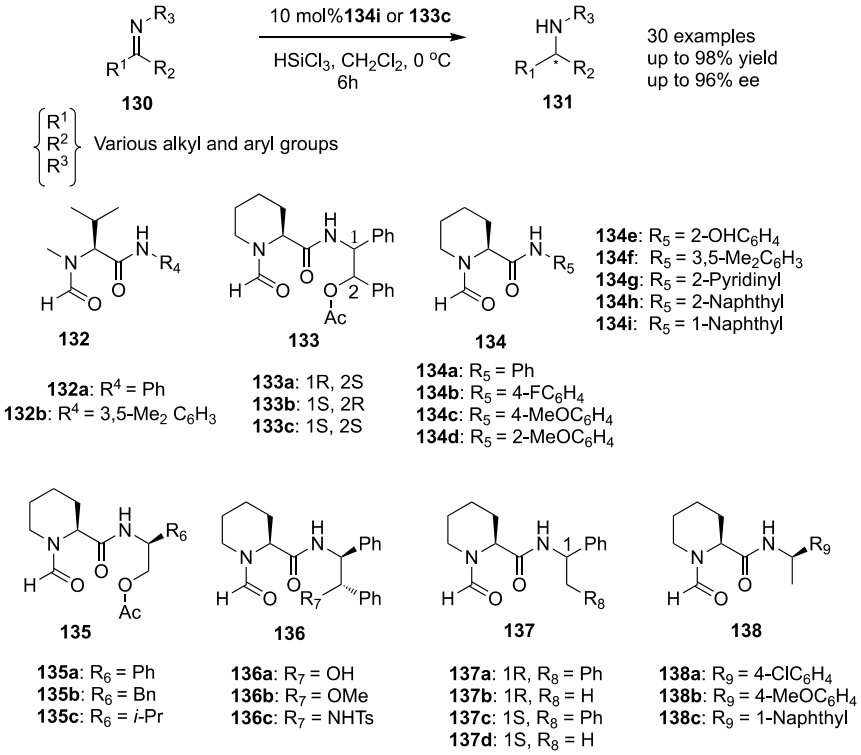
Scheme 38. Asymmetric epoxide ring opening with anilines.



Scheme 39. Probable catalytic cycle for epoxide ring opening.

2.8. Asymmetric Reduction of N-Aryl Imines

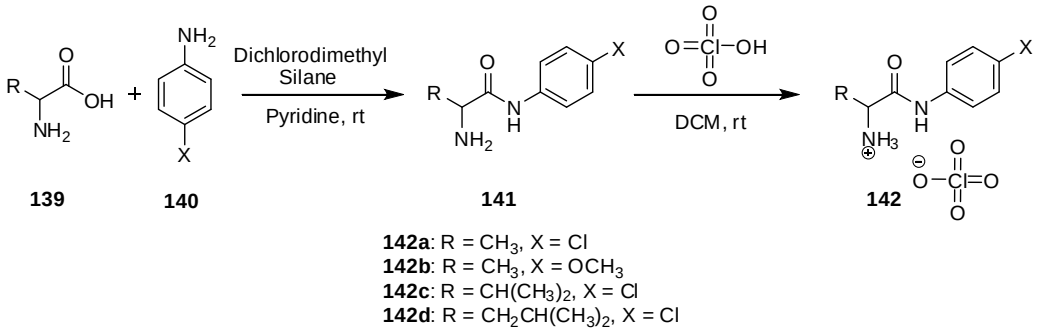
Zhouyu Wang et al. [104] created a variety of Lewis basic organocatalysts derived from L-pipecolinic acid for the enantioselective reduction of N-aryl ketimines utilizing trichlorosilane as the reducing agent. The investigation of the link between the structure of the side amide group and its catalytic performance yielded exceptionally potent catalysts (**132–138**). In particular, an arylamido-type catalyst (**134i**) and non-arylamido-type catalyst (**133c**) demonstrated high reactivity and enantioselectivity, allowing for the reduction of a wide range of N-aryl imines with high isolated yields (up to 98%) and *ee* values (up to 96%) under mild conditions, i.e., dichloromethane as a solvent at 0 °C temperature (Scheme 40). Previously, the **133c** catalyst was produced, and its catalytic efficacy was evaluated. They discovered that the best catalyst (**134i**), which is structurally simpler, easier to synthesize, and significantly less expensive than the previous catalyst (**133c**), exhibits nearly the same efficiency as **133c** and is applicable to difficult substrates containing a relatively bulky alkyl group that **133c** cannot tolerate. Furthermore, they thoroughly investigated the structure–efficiency relationship (SER), application breadth, and limitations of the catalytic system for this reaction.



Scheme 40. Asymmetric reduction of N-aryl imines.

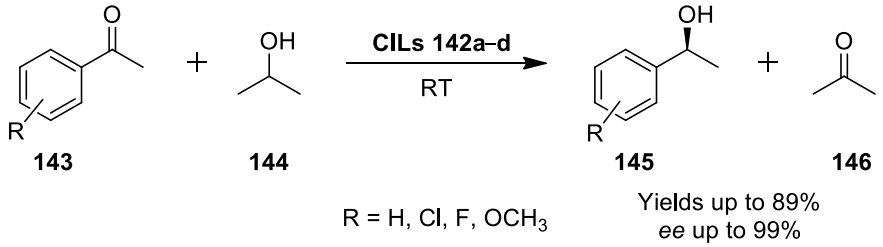
2.9. Asymmetric Hydrogen Transfer of Acetophenone

Asymmetric hydrogen transfer of ketones is one of the most effective and efficient methods for producing stereoselective chiral alcohols, which are essential building blocks for the production of chiral fine chemicals, medicines, agrochemicals, and bioactive natural products. Anil K. Kinage et al. [105] employed easy ways to create chiral amino-amide-based ionic liquids, which they then used as stereoselective organocatalysts in the asymmetric transfer hydrogenation of acetophenone at room temperature to produce chiral alcohols. The amino acid amides that comprise the chiral ionic liquids were synthesized in two steps. In the first stage, amino acid amides **141a–d** were produced in a single step at room temperature by amidation with dichlorodimethyl silane as a silylating agent and a chiral amino acid employing a simultaneous protection and activation method. The amino acid amides from the first step were protonated in the second step to produce chiral ionic liquids (CILs) **142a–d** (Scheme 41).



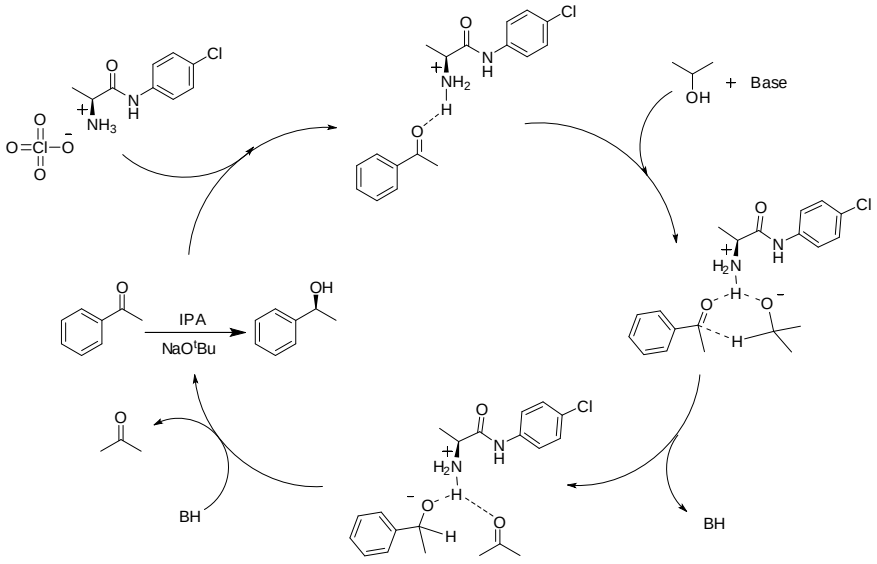
Scheme 41. Synthesis of chiral ionic liquids of amino acid amides.

The authors first investigated the catalytic activity of simple amino amides (**141**) for asymmetric transfer hydrogenation of acetophenone. However, even after 24 h, they did not acquire a result. Then, utilizing chiral ionic liquids of amino acid amides (**142**) as chiral sources, they obtained the corresponding asymmetric transfer hydrogenation of acetophenone products with good yields and outstanding enantioselectivity (Scheme 42).



Scheme 42. Asymmetric transfer hydrogenation of acetophenone utilizing chiral ionic liquids of amino acid amides.

Scheme 43 depicts the suggested reaction mechanism. The positively charged nitrogen atom from chiral ionic liquids of amino acid amide donates a proton to the oxygen atom of the carbonyl group of ketones, and the hydride anion is transferred to carbonyl carbon in an alkaline medium, resulting in the formation of chiral alcohols. The reusability of these ionic liquid catalysts was also studied, and up to three cycles were obtained with no yield or selectivity loss.



Scheme 43. Mechanism of asymmetric transfer hydrogenation of acetophenone utilizing chiral ionic liquids of amino acid amides.

3. Conclusions

In recent years, simple primary α-amino amides have become one of the most important classes of organocatalysts, owing to their simplicity of synthesis, the existence of adjacent bifunctional groups, and the availability of a variety of alternatives to strengthen the fundamental steric sites. Because they each contain two contiguous bifunctional groups, they are capable of universal base or acid activation via covalent and non-covalent ways of interaction with substrates. As organocatalysts, these simple primary α-amino amides are less costly alternatives to chiral diamines and cinchona-derived primary amines. Surendra Singh et al. (2019) and Pandey et al. (2011) published reviews on the catalytic efficiency of prolinamides as organocatalysts, and in 2009, Xiaoming Feng et al. reported on the catalytic efficiency of α-amino amides as organocatalysts. It is always a challenging task to investigate the applicability of simple types of organocatalysts such as α-amino amides in a variety of organic transformations. In this review, we discussed the recent catalytic efficiencies of α-amino amides and their single-step derivatives in aldol reaction, Strecker reaction, Michael tandem reaction, allylation of aldehydes, reduction of N-Aryl imines, opening of epoxides, hydrosilylation, asymmetric transfer of hydrogen, and N-specific reaction of nitrosobenzene with aldehydes (from 2011 to date). To our satisfaction, we have had the opportunity to contribute to this field, and we intend to continue searching for organocatalytic uses of simple α-amino amides. Owing to the existence of several functional groups and the simplicity of synthesis and operation, we expect that this type of primary α-amino amides will become a useful class of organocatalysts. We anticipate significant advancements in this field in the near future.

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