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MINI-REVIEW ARTICLE

Organocatalytic C-H Bond Functionalizations for the Synthesis of Heterocycles

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Abstract: Organocatalysis is an important and rapidly growing area for the synthesis of various organic molecules. Because of the inherent non-metal properties, mild reaction conditions, and broad functional group tolerance, the use of small organic compounds encoding and converting another organic component has developed into a remarkable process. C-H activation reactions, on the other hand, have already emerged as a powerful strategy for forming C-C and C-X (X= N, O, S) bonds. Combining organocatalysis and C-H bond functionalization is highly rational as two coexisting and rapidly growing research fields in modern synthetic chemistry, and the cooperative strength along this consistent has proven to be a successful way of making C-H bond functionalization much more feasible, reliable, and specific. At the same time, the synthesis of heterocyclic compounds is an important field in organic chemistry due to the vast application of heterocycles in pharmaceuticals, polymers, and material science. This mini-review describes the recent developments in the synthesis of heterocyclic compounds through the alliance of organocatalysis and C-H bond functionalizations.

Keywords: Organocatalysis, heterocycles, C-H bond functionalizations, hydride transfer, tert-amino effect, functional group.

1. INTRODUCTION

Organocatalysis is among the significant new approaches in synthetic organic chemistry that are now gaining a lot of attention and offering effective methods with amazing results [1, 2]. The phrases "organic" and "catalyst" are combined to form the term "organocatalyst". A harmless, low molecular weight organic molecule without metal is employed to catalyze the reaction in organocatalytic processes. The word "organocatalysis" [3, 4] refers to the method of accelerating chemical processes by adding a substoichiometric amount of an organic substance. The attention on this topic has increased rapidly in recent years, owing to both the uniqueness of the idea and, more crucially, the reality that several organocatalytic reactions fulfill the efficiency and selectivity criteria of known organic processes. The elements that make up the organocatalyst are carbon, hydrogen, nitrogen, oxygen, sulphur, and phosphorus, and can be either chiral or achiral. Organocatalysis offers several benefits, both in terms of its synthetic potential and from an economic point of view. Additionally, from both an ecological and economic perspective, the lack of metal in organocatalysts offers alternate and environmentally benign practical conversions. Organocatalytic reactions are progressively more useful in the building of various molecular frameworks [5-7]. Because of the intrinsic non-metal property, milder reaction conditions, as well as wide functional group tolerance, the utilization of small organic molecules susceptible to stimulating and converting another organic molecule has generated much interest. Organocatalysis is currently a prominent catalytic technique, comparable to metal [8-11] and enzymatic catalysis [12-15], and a novel strategy for C-C/C-X (X= N, O, S) bond formation is being explored in this field. C-H bond functionalization is a recent notable advancement in organic chemistry. Direct functionalization of the C-H bond is dominated by transition-metal catalysis, which has its roots in organometallic chemistry, while organocatalysis is mostly following behind.

The field of C-H bond functionalization is expanding quickly and is expected to keep pushing the boundaries of chemical reactivity, possibly leading to the perception of C-H bonds as pervasive functional groups shortly [16]. This versatility in C-H bond transformation opens up whole new avenues for extensive chemical synthesis [17-21]. From a topological standpoint, the direct ways of building molecules are immediately obvious and should result in a significant streamlining of synthetic processes. Because innovative synthetic techniques influence not only how we produce the required molecules but also what we produce and investigate, they will also influence the implementation of synthetic methods in many other areas of science.

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Current Organocatalysis

By immediately establishing new carbon-carbon and carbon-hetero-atom bonds from prevalent C-H bonds without first activating the substrates, C-H bonds can be functionalized at an atom- and step-economic outlay. The efficient and practical transformation of a particular C-H bond remains a difficult problem despite the dramatic advancements shown over the past 20 years. The reasons are dual: (1) There are many strong C-H bonds, and (2) harsh conditions are frequently required. Taking into account, the known bond energies of the major organic molecules suggests that all C-H bonds have substantial bond energy compared to carbon-carbon and carbon-hetero-atom bonds and have fewer thermodynamically distinct properties [22]. Previously, C-H bonds were considered chemically inert bonds. Normally, inertness is assessed solely by taking into account the pKa of a certain C-H bond. But an acidic C-H moiety with a lower pKa might be homolytically potent with a higher bond dissociation energy(BDE), or the opposite might be true. Additionally, the recent resurgence of photocatalysis may further obfuscate the distinction between "inert" and "reactive," as an inert C-H bond's ground state might transform into one that is very active when activated by photoinduced energy/electron transfer processes [23]. Although a distinct boundary is difficult to establish, it is usually accepted that organocatalysis operates primarily with reactive C-H bonds (pKa 30).

In organic chemistry, heterocycles and their production, conversion, and properties are crucial. Heterocyclic moiety(s) are present in the majority of pharmaceuticals, natural products, agrochemicals, additives, conductive polymers, and other functional materials [24-30]. New medicinal substances are frequently made to have a better pharmacokinetic profile to boost their ligand effectiveness. In general, 70% of all pharmaceuticals and agrochemicals have at least one heterocyclic ring. The main factor influencing the medication heterocyclic scaffold, which commonly has a positive impact on its synthetic accessibility and physicochemical properties, is what brings lipophilicity and solubility values into the appropriate balanced range regarding absorption and bioavailability. This is one of the main reasons for the enormous usefulness of heterocycles in pharmaceuticals. As a result, scientists are always exploring new and effective techniques for synthesizing heterocyclic compounds.

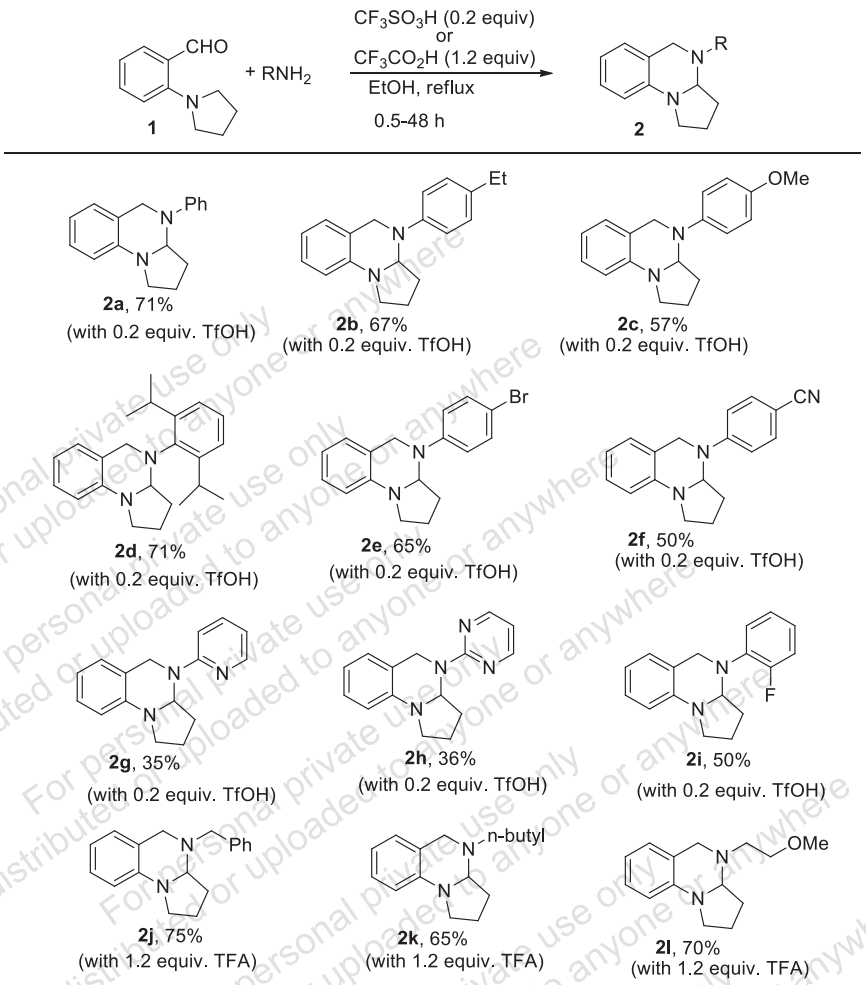
The combination of organocatalysis and C-H bond functionalization is well anticipated as two coexisting and rapidly expanding areas of research in contemporary synthetic chemistry, and the combined strength of this connection is a strategic tool in improving C-H bond functionalization's viability, predictability, and chemo- and stereoselectivity. Therefore, we firmly think that a careful review of this subject-specifically, organocatalysis in C-H bond functionalization for heterocycle synthesis-is both necessary and highly desired. In this regard, one nice and elegant review by Sarkar and Mukhopadhyay [31] on the organocatalytic synthesis of heterocycles inspired us to write this mini-review.

2. RESULTS AND DISCUSSION

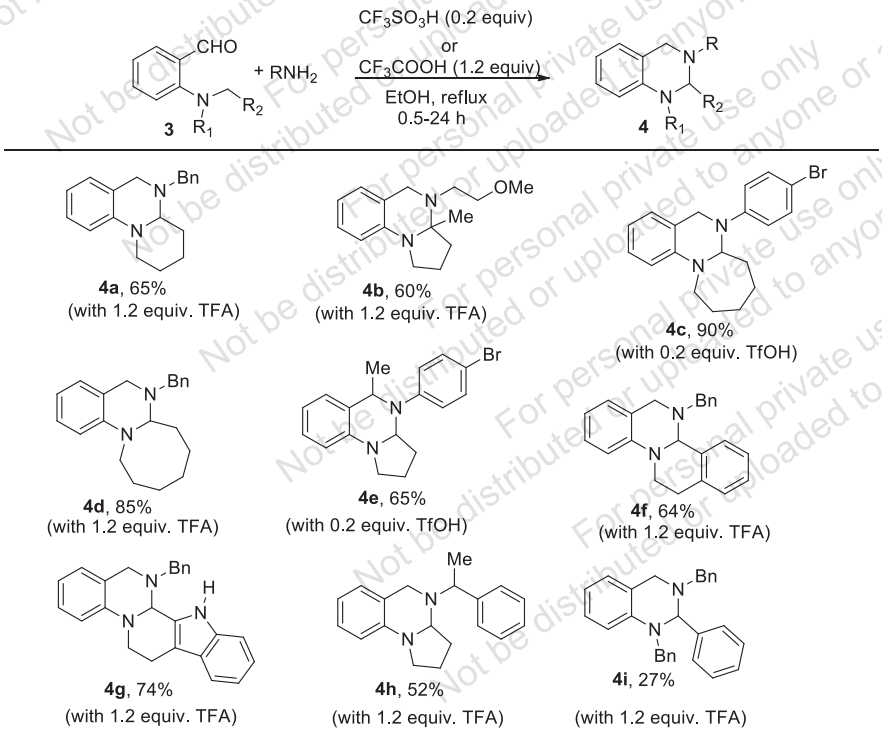
An area of keen importance is the functionalization of comparatively unreactive C-H bonds to produce functional materials and medicinally active molecules. As an illustration C(sp^3)-H bond activation has drawn a lot of interest due to its ability to readily create molecular complexity and speed up the formation of important molecules. The tert-amino effect also offers an intriguing method for C-H functionalization for the synthesis of complex organic molecules. These processes frequently include an internal redox isomerization that involves the migration of hydrides from the amino alpha-carbon.

In 2009, Meth-Cohn *et al.* described simple single-flask processes for synthesizing aminals from o-aminobenzaldehydes and aromatic or aliphatic amines. They have demonstrated that Bronsted acids can speed up processes involving the "tert-amino effect" [32-34]. This makes it possible to synthesize, under benign conditions, species of potentially valuable and hitherto unknown aminals that are not easily accessible by other methods. In their investigation, they discovered that the mixture of triflic acid (0.2 equivalents) and ethanol offered a reliable technique for the synthesis of cyclic aminals (Scheme **1**). Different amines were used to test the reaction, and moderate to good yields (35-75%) were achieved [35]. To get satisfactory yields of the desired compounds, a stoichiometric quantity (1.2 equivalents) of trifluoroacetic acid was required in some cases. As for amines various substituents (-Et, -OMe, -CN, -Br, -F, -$CHMe_2$) at different positions of the benzene ring were well tolerated and desired products were obtained in good yields. Heteroaromatic amines such as 2-pyridyl and 2-pyrimidyl amine as well as aliphatic amines also participated in this reaction. Sterically crowded aniline, namely 2,6-diisopropyl aniline also nicely react under this protocol and afforded the desired product in 71% isolated yield using 0.2 equivalent triflic acid as an organocatalyst. Scheme **2** shows the scope of this acid-promoted redox procedure with consideration of the aminobenzaldehyde part. Numerous structurally varied aminobenzaldehyde successfully provide the desired aminals through the reaction with primary amines omnipresence of 0.2 equivalent of TfOH or stoichiometric amount of TFA as a catalyst.

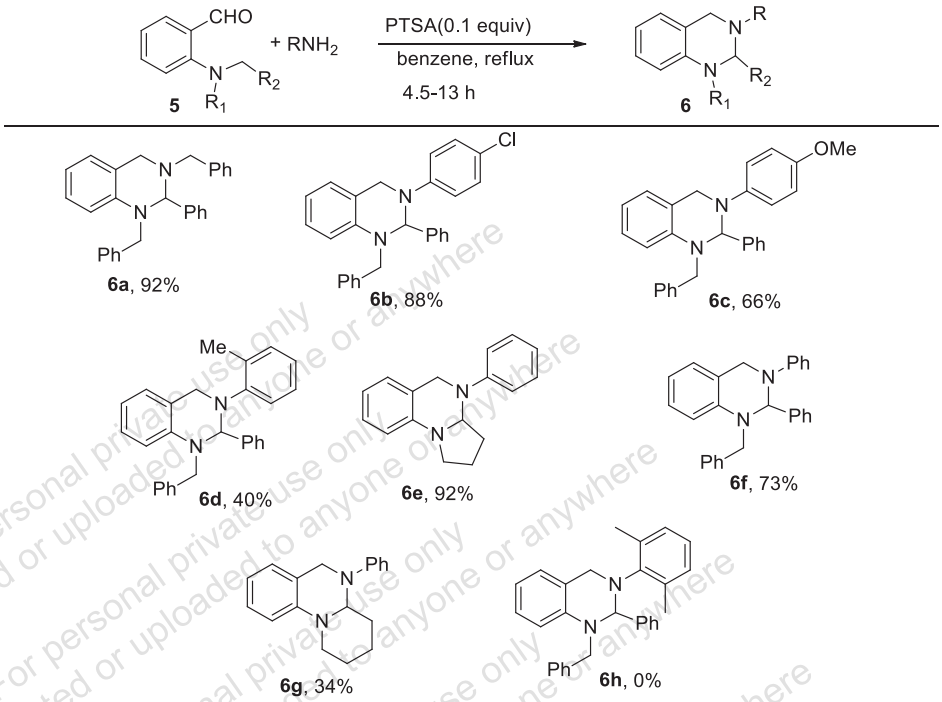
After Seidel's pioneering work, in the same year, Mori *et al.* reported the various organocatalytic acid-catalyzed synthesis of aminals (Scheme **3**) [36]. Compared to the several Bronsted acids, para-toluene sulfonic acid (PTSA) was found to be the most effective catalyst for these transformations. Structurally different amines were used in this reaction under optimized conditions, which provided the cyclic aminal products with moderate to good yields. Aromatic amines with various substituents (-Cl, -OMe, Me), and aliphatic amines are well tolerated under this protocol. Sterically hindered aromatic amines such as 2,6-dimethyl aniline did not participate in the reaction. The authors proposed a plausible mechanism for this reaction as depicted in Scheme **4**. Firstly, amine reacted with the aldehyde group through a condensation reaction to form an imine. Secondly, the 1,5-hydride shift of protonated imine in the presence of Bronsted acid provides an imino-amine intermediate. Lastly, the generated imino-amine intermediate was cyclized to form the desired cyclic aminal.



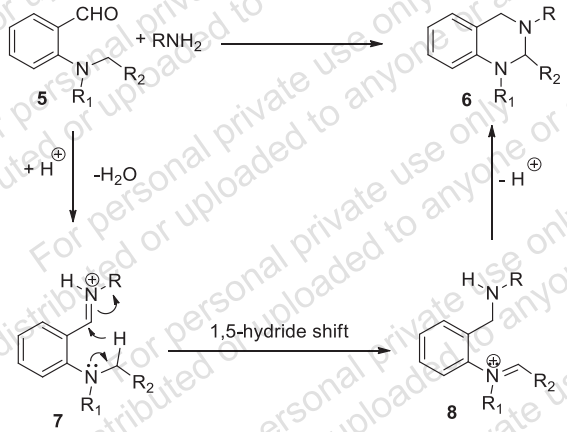
Scheme 1. Acid-catalyzed synthesis of cyclic aminals from pyrrolidine containing o-aminobenzaldehydes.



Scheme 2. Acid-catalyzed synthesis of cyclic aminals from various aminobenzaldehyde component.



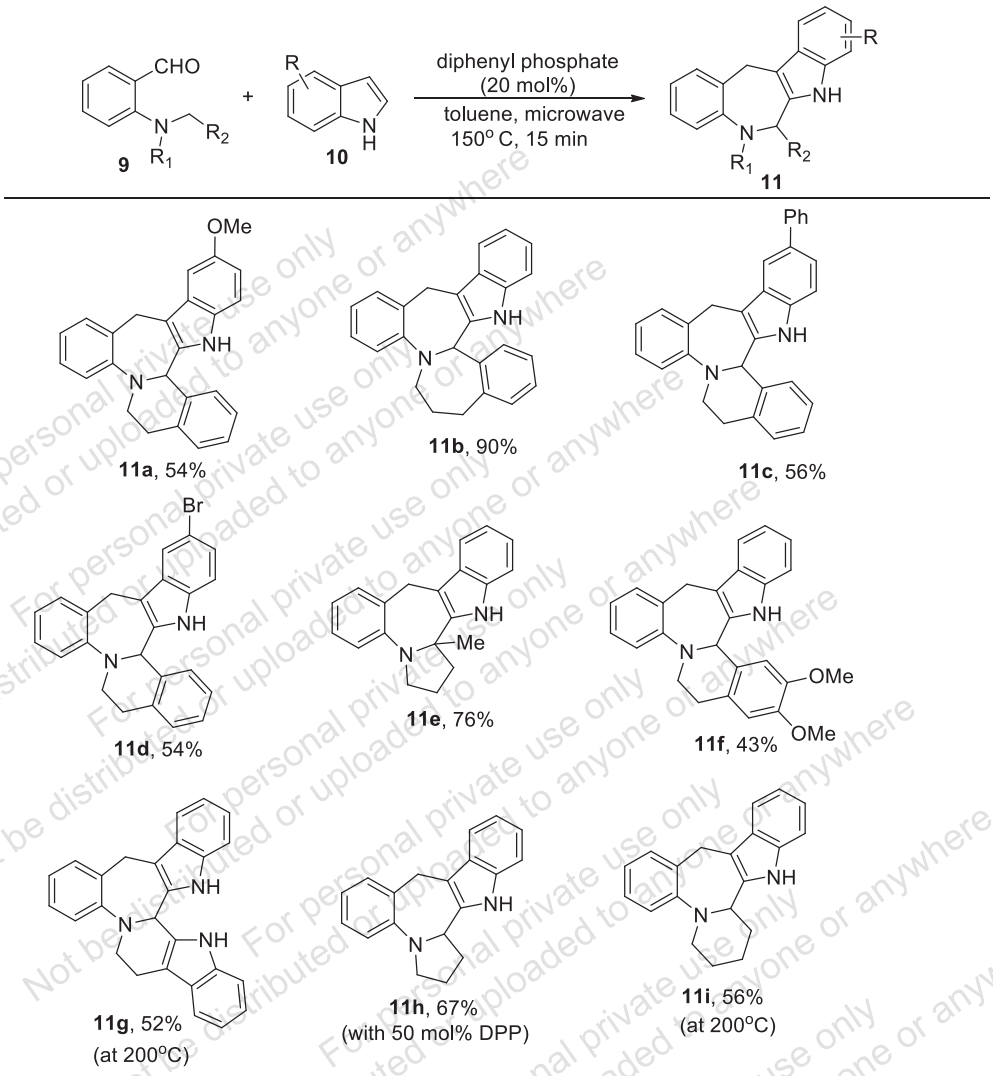
Scheme 3. PTSA catalyzed synthesis of quinazolines.



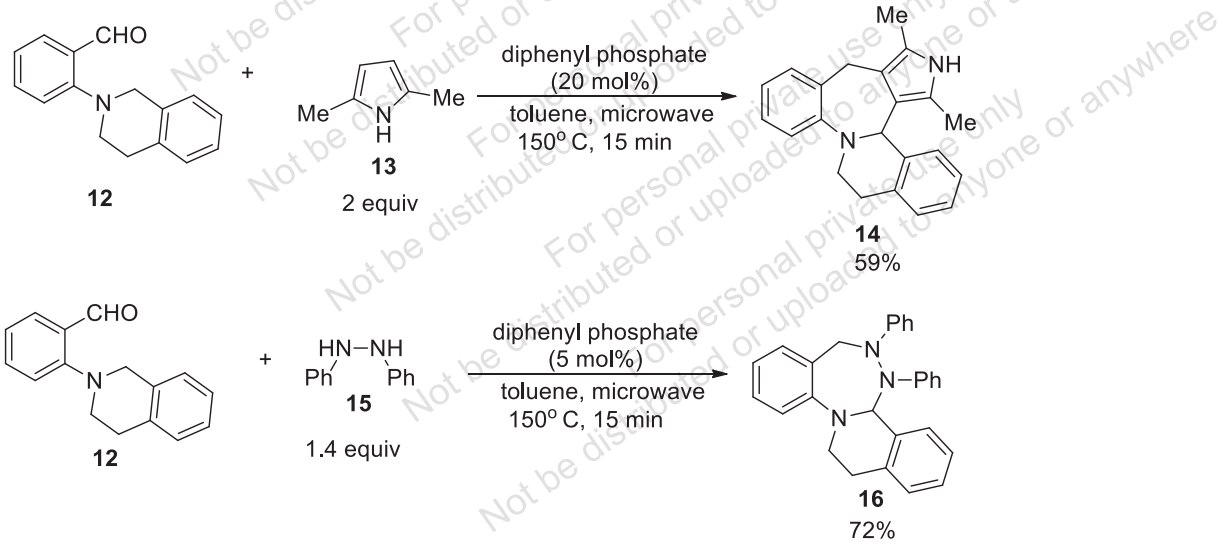
Scheme 4. Plausible mechanism for acid-catalyzed quinazoline synthesis

Haibach *et al*., (2011) documented an elegant work on the cascade reaction of aminobenzaldehyde with indoles to produce indole-fused cyclic amine compounds in good yields, two years after their first report on organocatalytic cyclic aminal synthesis (Scheme **5**) [37]. This reaction proceeds through the condensation, 1,5-hydride shift, and is followed by a ring-closure sequence. In this protocol, polycyclic azepinoindoles and related heterocycles can be accessible in good to excellent yield through a one-step sequential cascade method. In particular, in this method, 20 mol% diphenyl phosphate was used as an efficient acid catalyst in toluene solvent under microwave conditions to obtain the desired products in a very short time (15 min). As expected, reaction under microwave reduces the reaction times compared to the normal thermal heating conditions due to the dielectric heating process [38]. Various electronically and structurally diverse indoles are nicely coupled under this protocol. Broad substrate scope, high yields, and easy and fast reactions are the merits of this protocol.

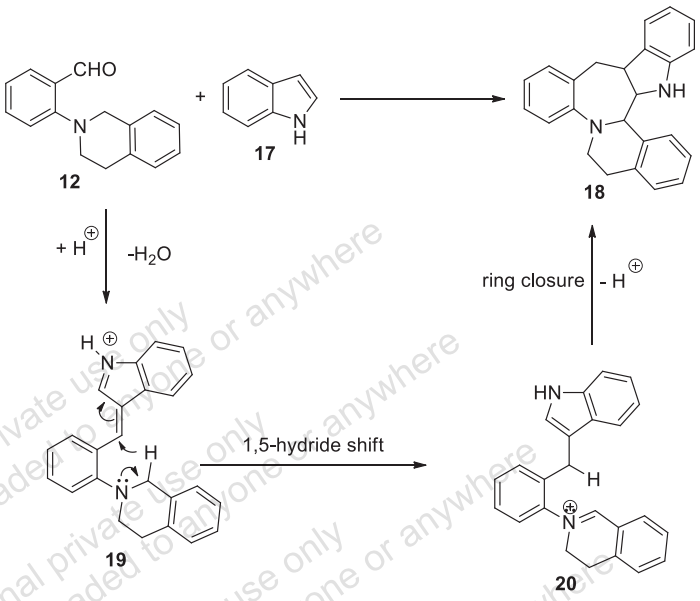
To get a satisfactory product yield for some substrate molecules, 50 mol% catalyst loading was necessary. Additionally, the authors effectively extended the scope of this protocol by the application of double nucleophiles, like 2,5-dimethylpyrroles and N,N'-diphenylhydrazine, and they provided the desired annulation product in good yields (Scheme **6**). They also suggest a plausible mechanism for this annulation cascade reaction, which is shown in Scheme **7**, using indole as a double nucleophile. Initially, indole reacts into the activated aldehyde group through a 3-position in presence of an acid catalyst and the elimination of the water molecule produces the vinylogous iminium (azafulvenium) ion. Next 1,5 hydride shift generates the new iminium ion which undergoes ring closure to obtain the desired annulated product.



Scheme 5. DPP-catalyzed annulations cascade reactions with indoles.

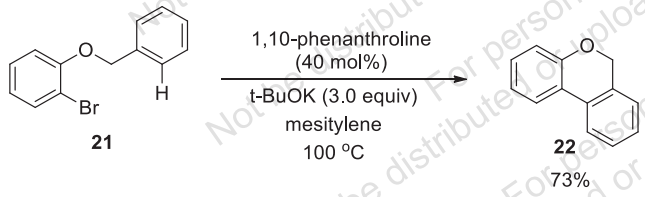


Scheme 6. DPP catalyzed annulations cascade reactions with 2,5-dimethyl pyrrole and N, N'-diphenylhydrazine.



Scheme 7. Plausible mechanism for DPP catalyzed annulations cascade reactions with indole.

Sun *et al.* reported an organocatalytic arylation reaction of aryl iodides and aryl bromides using 1,10-phenanthroline as an organocatalyst at 100°C [39]. In their protocol, 40 mol% 1,10-phenanthroline and 3.0 equivalents of t-BuOk as a base were used in the case of bromides. In that study, they investigated an intramolecular version of their reaction using 1-(benzyloxy)-2-bromobenzene as the substrate and obtained cyclic ether [40] in good yield (Scheme **8**).



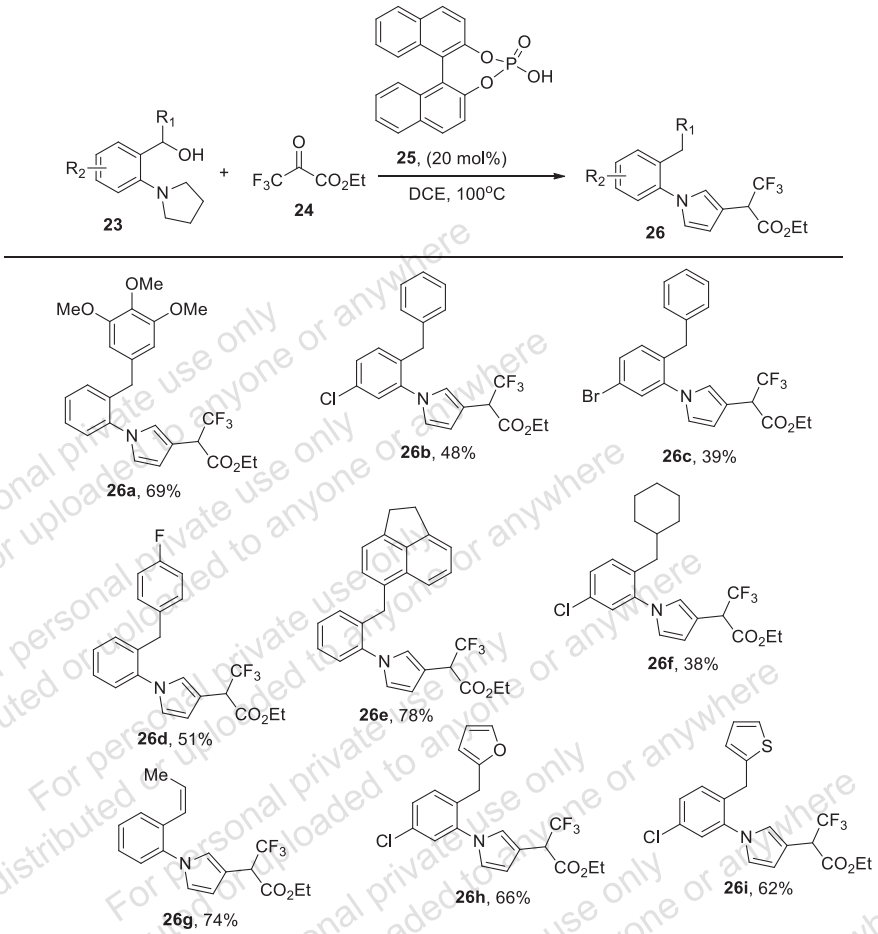
Scheme 8. Organocatalytic synthesis of cyclic ether.

The pyrrole moiety is a crucial structural component of bioactive compounds and natural products [41]. Arylpyrroles make a significant contribution among such well-known chemical frameworks, acting as chiral resolving agents, ligands, and catalysts. The production of these structures has therefore received a lot of interest. However, most approaches for synthesizing pyrrole derivatives are restricted to producing multi-substituted pyrroles and pyrroles that have been α-functionalized. As a result of their intrinsically weaker nucleophilicity, especially in comparison to the pyrrole's α-position, β-substituted pyrroles have lagged far behind in the advent of strategies to access them.

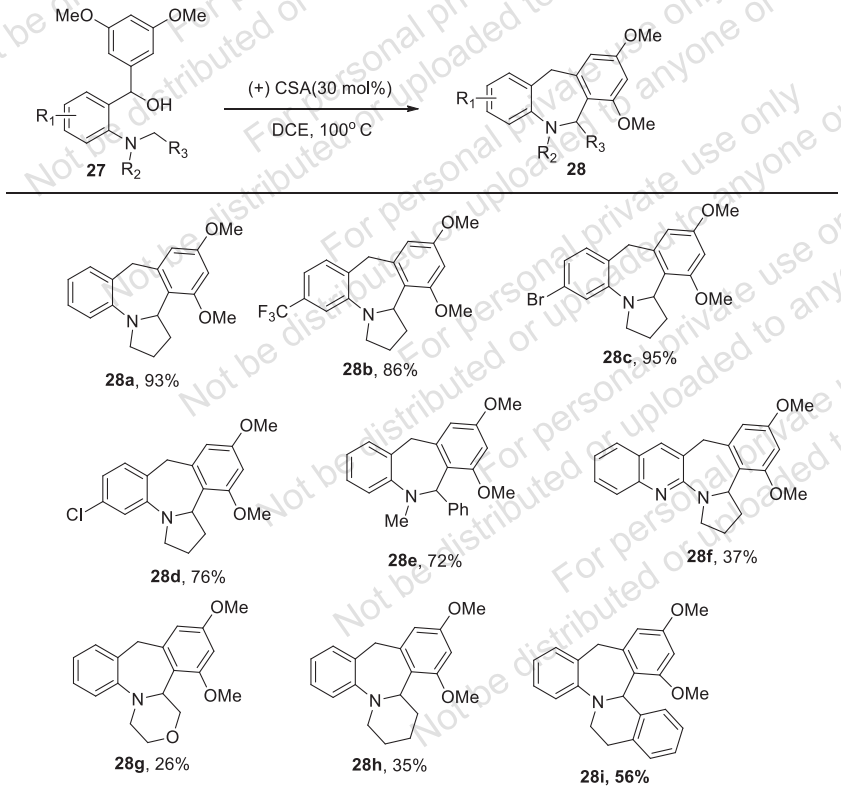
Zhou *et al*., 2020 demonstrated a unique strategy for the synthesis of substituted pyrroles by functionalizing and aromatizing pyrrolidines through the application of a new hydride transfer-triggered cascade reaction (Scheme **9**) [42]. Starting from N-aryl pyrrolidines, various trifluoromethyl-substituted N-aryl pyrroles were synthesized in one step. A number of different substituents (-Me, -OMe, -F, -Br, Cl) and heterocycles (thiophene, furan) in the aminol part are well tolerated and provide the expected products in good yields. A new and novel dehydrogenative aromatization reaction triggered by organocatalyst has been described by the authors in that report. Additionally, the feasibility of nitrogen-C (sp^3)-H bond to act as a suitable hydride donor was documented there for the first time.

In 2018, Li *et al.* reported the carbocation-initiated cascade [1,5]-hydride transfer/cyclization and dimerization process for the synthesis of dihydrodibenzo[b,e]azepine and octahydrodipyrroloquinoline derivatives in good yields through a redox-neutral functionalization of C(sp^3)-H bonds (Scheme **10**) [43]. In this protocol (+)-10-camphor sulfonic acid ((+)-CSA) was used as a catalyst. Although the reaction can proceed in water, however, it produces the desired product in low yield. Thus, the use of anhydrous dichloroethane at high temperatures in presence of 30% (+)-CSA was found to be the optimal condition. Interestingly, both electron-rich and electron-deficient substituents were all tolerated under this protocol. Various substituents (-Me, -Ph, -Cl, -Br, -CF_3) at different positions of the aromatic ring were well tolerated and provided the desired product in good yields. Notably, the substrate molecules containing acyclic amines which were found to be unsuitable in many hydride transfer reactions nicely participated in this intramolecular redox reaction and provides the desired product in good yields. The beauty of this cascade protocol is that it is a transition-metal-free process with high atom- and step-economy, as well as water was formed as an environmentally benign byproduct.

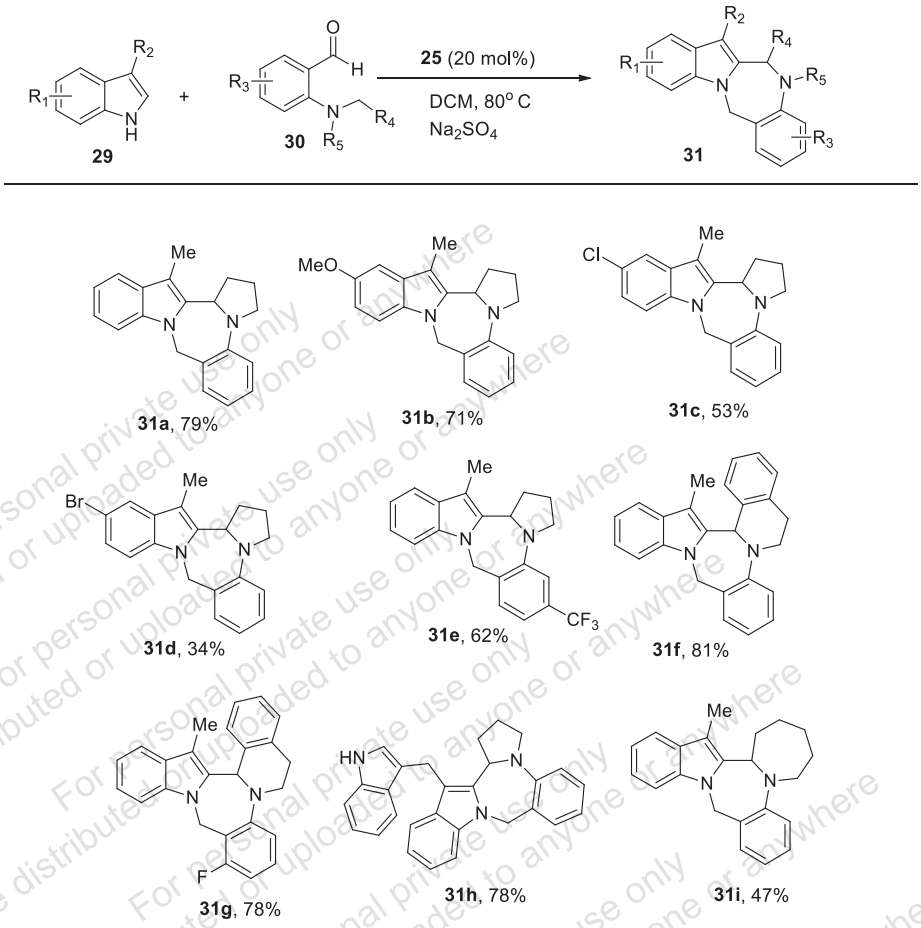
In 2019, Wang *et al.* reported a new and innovative method for redox-neutral [5+2] annulation of 3-alkyl indoles with ortho-aminobenzaldehyde to produce indole-1,2-fused 1,4-Benzodiazepines (Scheme **11**) [44]. The reaction proceeds through a cascade of sequential N-alkylation, and dehydration followed by [1, 5]-hydride transfer and Friedel-Craft alkylation. Various structurally diverse indole-1,2-fused 1,4 Benzodiazepines were obtained in moderate to



Scheme 9. Organocatalytic cascade β-functionalization/aromatization of pyrrolidines.



Scheme 10. Organocatalytic carbocation-initiated cascade [1,5]-hydride transfer/cyclization reactions.



Scheme 11. Organocatalytic [5+2] annulation of 3-alkylindoles with o-aminobenzaldehydes.

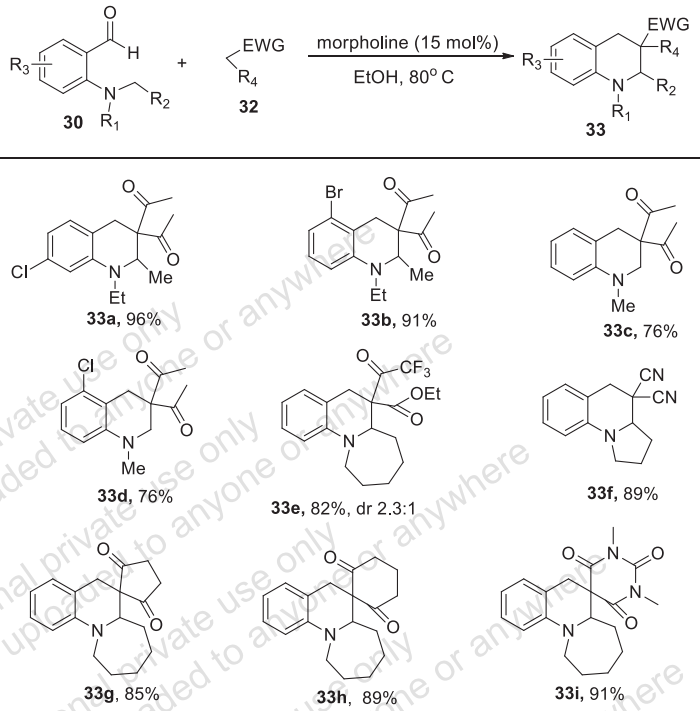
good product yields. Various alkylindoles containing both electron-donating (-OMe, -OBn, -Me) and electron-withdrawing (-F, -Cl, -Br) groups react smoothly in this protocol. Not only that, ortho-aminobenzadehydes substituted with various functional groups such as -F, -Cl, -Br, -Me, -CF_3 are well tolerated and produced desired products in good yields. Large substrate scope, high functional group tolerance, high step-economy, metal-free conditions, and high regioselectivity are the merits of this protocol. This protocol was also found to be suitable for the gram-scale synthesis of the desired products. Although, 2-morpholinobenzaldehyde and indoles substituted at the C3 position with highly electron-withdrawing groups like -NO_2, -CN, -CHO did not provide the expected products.

Yang *et al.* demonstrated an innovative strategy for the synthesis of tetrahydroquinolines through the morpholine-catalyzed hydrogen-bonding assisted [1,5]-hydride transfer process (Scheme **12**) [45]. The o-aminobenzadehyde derivative reacts with the compounds containing active methylene groups which react nicely under this organocatalytic method. Both acyclic and cyclic o-aminobenzaldehydes decorated with various substituents in the aromatic rings were successfully coupled with a variety of compounds bearing active methylene groups. The authors also effectively used this protocol for the synthesis of the novel antibiotic drug PNU-286607. Furthermore, this protocol was also found to be applicable to the gram-scale synthesis of tetrahydroquinoline derivatives with good yields and high efficiency.

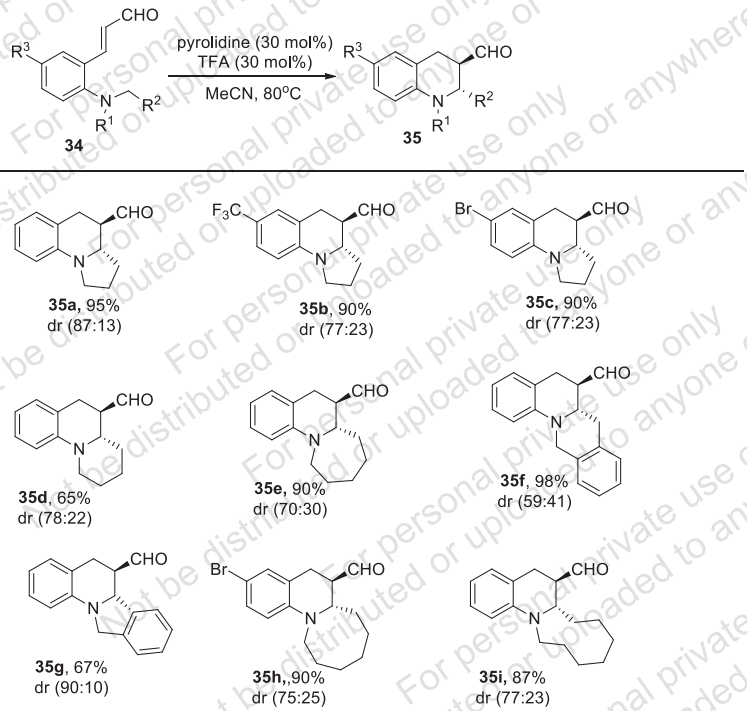
3. ASYMMETRIC SYNTHESIS *VIA* C-H ACTIVATION

In addition to enzymes and metal-based catalysts, asymmetric organocatalysis—where chiral organic molecules serve as efficient catalysts for stereoselective organic transformation has emerged as a third fundamental pillar of asymmetric catalysis and has found a place in the toolkits of researchers working on both small-scale and large-scale projects. Numerous important accolades, like the 2021 Nobel prize in chemistry given to Benjamin List and David MacMillan for "the discovery of asymmetric organocatalysis," have helped to draw attention to the field's fast improvement, which has mostly occurred during the recent two decades [46].

Due to the vast range of pharmacological characteristics that quinolines and tetrahydroquinolines possess, they have attracted much attention [47-49]. Kang *et al.* reported the asymmetric version of the organocatalytic C-H activation process for the first time in the preparation of chiral tetrahydroquinolines (Scheme **13**) [50]. These amino catalytic intramolecular redox reactions used ortho-(Dialkylamino) cinnamaldehydes as suitable substrates. Initially, they estab-



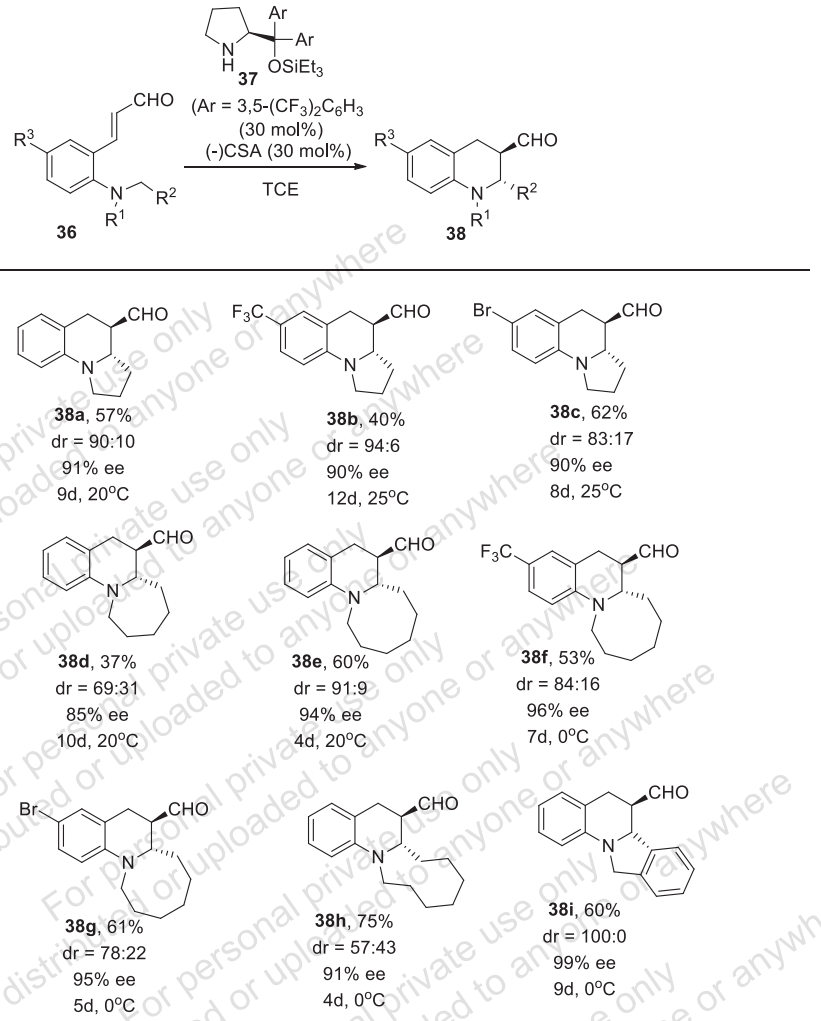
Scheme 12: Organocatalytic redox-neutral synthesis of tetrahydroquinolines.



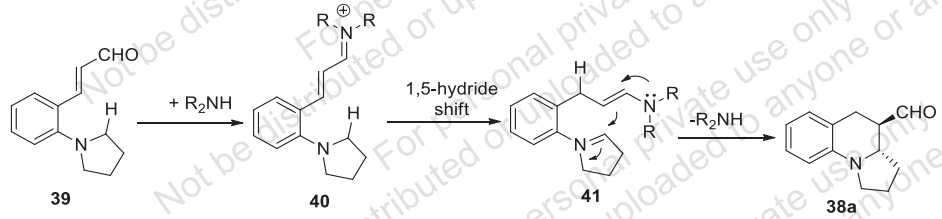
Scheme 13: Organocatalytic non-asymmetric variant of tetrahydroquinolines synthesis.

lished a non-asymmetric variant of the reaction using pyrrolidine-trifluoroacetic acid as a catalyst in an acetonitrile solvent. For amine donors with varying ring sizes, high yields (67-98%) and good to excellent diastereoselectivities (59:41-80:20) were achieved. The authors began the asymmetric transformation using chiral secondary amine catalysis after completing the non-asymmetric synthesis of tetrahydroquinolines using the C-H activation technique.

After investigating several chiral amines as catalysts, solvents, acid additives, and temperature combinations, the chiral pyrrolidine catalyst was found to be the best catalyst, and 1,1,2 trichloroethane (TCE) was found to be the suitable solvent at 20°C and produced the required product with the best enantioselectivity (89% ee). The optimized conditions resulted in the production of chiral tetrahydroquinoline products with satisfactory yields (37-75%), moderate to excellent diastereoselectivities (57:43 to 100:0 dr), and good



Scheme 14: Organocatalytic asymmetric variant of tetrahydroquinoline synthesis.



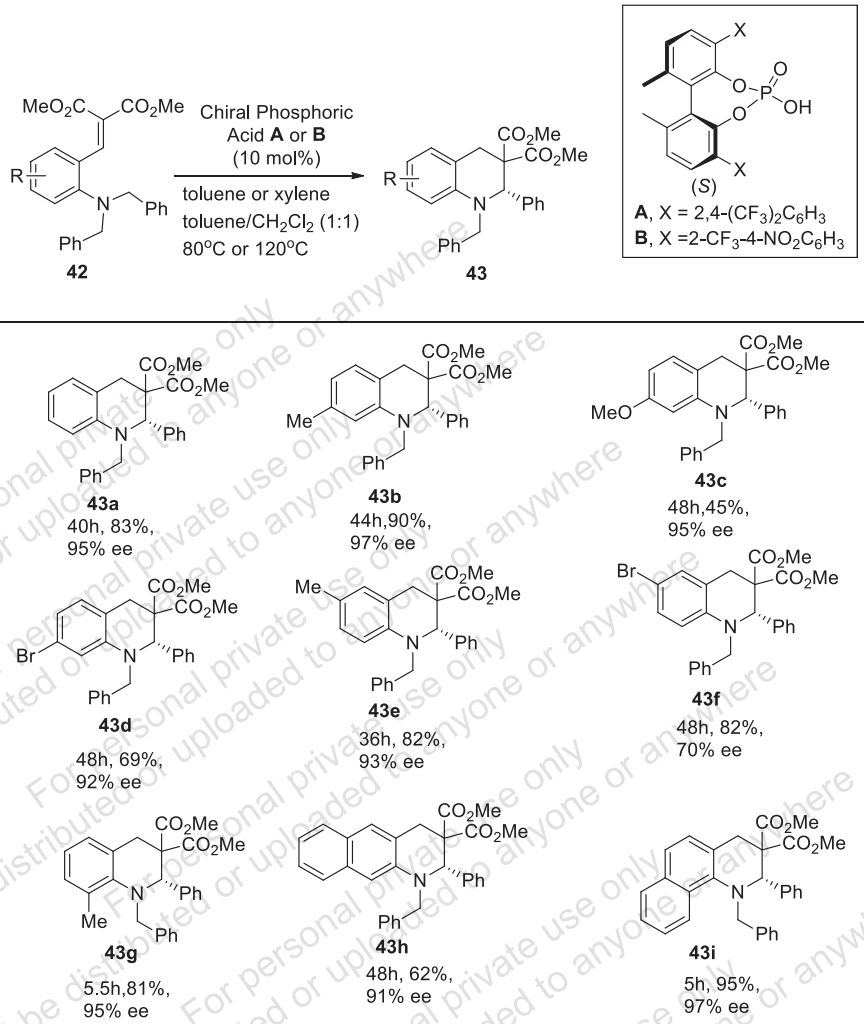
Scheme 15: Plausible mechanism for organocatalytic reaction of ortho-(dialkylamino)cinnamaldehydes.

enantioselectivities (85-99% ee) (Scheme **14**). The reaction temperature was decreased to 0 or 20°C for some particular substrates to achieve excellent enantioselective reactions. The authors also reported a plausible mechanism for this reaction, which is shown in Scheme **15**. An iminium ion is initially produced when the secondary amine catalyst interacts with the unsaturated aldehyde. The equivalent enamine is produced by the following 1,5 hydride shift. Lastly, the product was produced *via* Mannich-type cyclization with the regeneration of the catalyst (Scheme **15**).

In 2011, Mori *et al.* reported a pleasant report for the asymmetric synthesis of substituted tetrahydroquinolines employing chiral phosphoric acid as the organocatalyst using benzylidene malonates as the hydride acceptor [51]. Additionally, a significant aspect of this work is the main use of N,N-dibenzylamine as the amine donor in this protocol rather than cyclic tertiary amines as previously reported by the Kim group. Mori *et al.* utilized biphenyl-based chiral phosphoric acid as catalysts and moderate to high product yields (45-95%) were obtained with excellent enantioselectivities (70-97% ee) were attained for various tetrahydroquinoline products containing gem-methyl ester groups (Scheme **16**).

CONCLUSION

For the production of different organic compounds, organocatalysis is a significant and constantly expanding field. Chemical processes can be sped up using organocatalysis,



Scheme 16: Organocatalytic asymmetric synthesis of tetrahydroquinolines having gem-methyl ester groups.

which employs small organic molecules mostly made of C, H, O, N, S, and P. When relative to (transition) metal catalysts, the benefits of organocatalysts comprise their lower sensitivity towards oxygen and moisture, their easy availability, low cost, and low toxicity, which offer a significant direct benefit in the manufacture of pharmaceutical intermediates. On the other hand, C-H activation processes have already become a potent method for creating carbon-carbon and carbon-heteroatom bonds. Organocatalysis and C-H bond functionalization are two synchronized and continuously expanding research areas in contemporary synthetic chemistry, and their combination makes C-H bond functionalization considerably more practical, dependable, and specific. This brief overview discusses recent advances in the combination of organocatalysis and C-H bond functionalizations for the synthesis of heterocyclic molecules; wherever necessary, the mechanistic discussion is also included to get a clear picture of the reactions.

LIST OF ABBREVIATIONS

PTSA = Para-Toluene Sulfonic Acid

TCR = Trichloroethane

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest financial or otherwise.

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