XII. Asymmetric Organocatalysis in Total Synthesis

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XII.1 Introduction

There is no doubt about the importance of natural products in chemistry, biology, and medicine, consequently their obtainment has always been a theme of interest for chemists. This was traditionally centered in their direct extraction from natural sources, and later the value of natural product synthesis has become questionless. Usually these compounds present stereogenic carbon centers and therefore, their syntheses must involve ways of getting chirality. Chiral pool and resolution of racemates represented the two principal strategies until the birth of asymmetric catalysis [1], which has revolutionized the chemical synthesis. In this context, asymmetric organocatalysis [2] appeared in the first decade of 21st century as a promising powerful tool, complementing metal and enzymatic catalysis. Since seminal works [3], this field has exponentially grown due to its main advantage: simplicity. And although the synthesis of complex molecules is still an active challenge in organocatalysis, there are already a high number of those syntheses where organocatalyzed reactions play a crucial role, showing its efficiency with elegance. In this recapitulation we will describe several selected examples published in the most recent years [4]. Moreover, this chapter is divided into different sections according to the most important modes of activation such as enamine and iminium catalysis, Brønsted acid and hydrogen bond catalysis, cinchona alkaloid catalysis, and phase transfer catalysis.

XII.2. Aminocatalysis in Natural Product Synthesis

Within organocatalysis, aminocatalysis has represented a key approach in a high variety of fundamental transformations [5]. Since the pioneering works reported contemporaneously by List [3a] and MacMillan [3b] in 2000, numerous have been the outcomes achieved in this appealing area. In the last twelve years many research groups have used secondary and, more recently, primary chiral amines which have become privileged structures as organocatalysts (Fig XII.1).

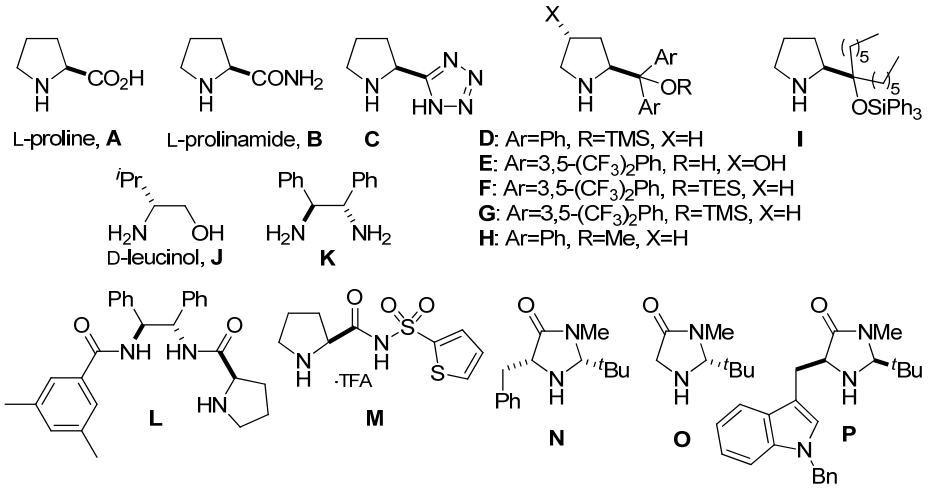


Figure XII.1 Chiral amines used as organocatalysts in natural product synthesis.

XII.2.1 Enamine Catalysis

The condensation reaction between an amine and an enolizable carbonyl compounds rapidly affords reactive enamines as nucleophilic intermediates, which have the capacity to react with an extensive range of electrophiles rendering the corresponding α-functionalization of those carbonyl compounds [6]. Since the pioneering work reported by List *et al.*[3a], in the last decade this mode of activation has witnessed an explosive growth in the field of organocatalysis. It is easy to find in the literature, many examples of application in total synthesis of this catalysis through different reactions (Fig XII.2). One of the most extensively explored has been aldol reaction, key step in the syntheses of callipeltoside C [7], convolutamydine A, B, E [8], (+)-przewalskin B [9], (−)-salinosporamide A [10], (+)-spongistatin 1 [11], (*S*)-(−)-3-butylphthalide [12], and (−)-anominine [13] among many other examples. The Mannich reaction, a classical method for the creation of new C-C bonds, can be found in the synthesis of natural products, such as (2*S*,3*R*,4*S*)-4-hidroxyisoleucine [14]. Furthermore, α-heterofuntionalization of carbonyl compounds *via* enamine activation has also been applied in the synthesis of natural products. Among other examples, α-oxidation is the most frequent one: 7,8-*O*-isopropylidene iriomoteolide-3a [15], (+)-neosymbioimine [16], (+)- and (−)-disparlure [17], (−)-(5*R*,6*S*)-6-acetoxy-5-hexadecanolide [18], and Hagen's gland lactones [19]; followed by α-amination: chloptosin [20], (*S*)-AIDA [21], and *Licopodium* alkaloids [22]. Sometimes α-heterofuntionalization of carbonyl compounds is necessary to form a temporal reactive intermediate, as is the case of α-selenylation: (+)-symbioramide [23], and α-chlorination: ripostatin B [24]. Moreover, organocatalytic Michael addition is other main C-C bond-forming strategy widely used in natural product synthesis. Illustrative examples are the syntheses of (+)-polyanthellin A [25], (+)-simplactone B [26], biyouyanagin A [27], (−)-oseltamivir [28,29], and ABT-341 [29,30] (Fig XII.2).

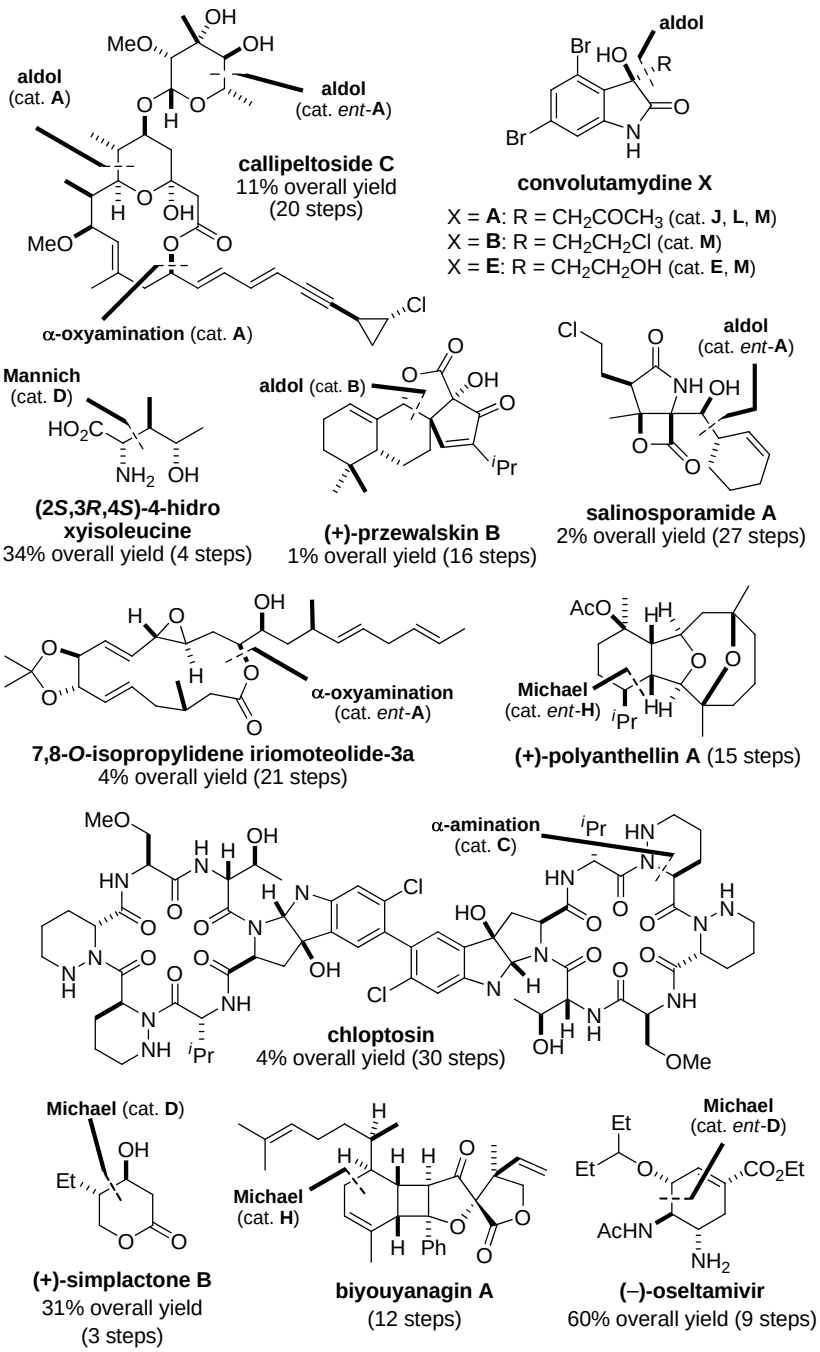
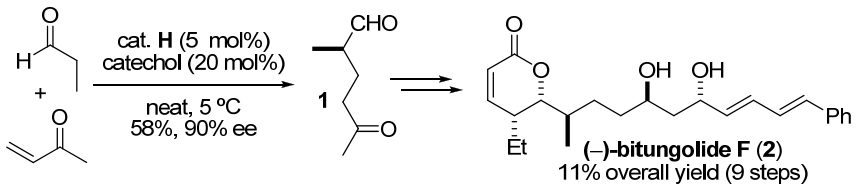


Figure XII.2 α-Funtionalization of carbonyl compounds *via* enamine catalysis applied in total synthesis.

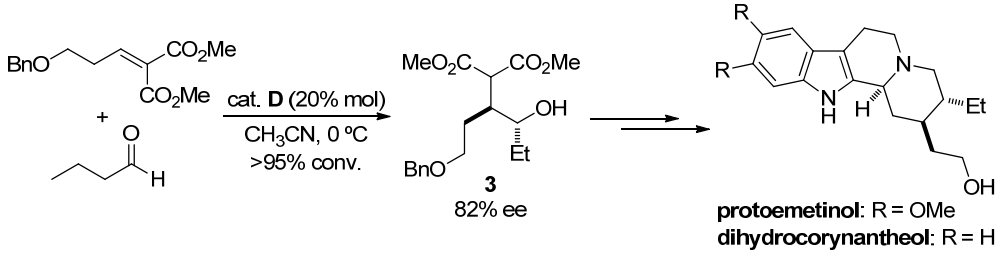
As an application of this enamine activation we describe the organocatalytic step in the construction of (–)-bitungolide F (**2**) skeleton recently published by Cossy and co-workers (Scheme XII.1) [31]. This natural product is a polyketide isolated by Tanaka *et al.* [32] from the Indonesian sponge *Theonella cf. swinhoei* that exhibits cytotoxic effects against 3Y1 rat normal fibroblast cells and inhibition toward VH1-related (VHR) dual-specificity phosphatase. The total synthesis of **2** starts with a previously reported enantioselective organocatalyzed Michael

addition [33] providing enantioenriched aldehyde **1**, key intermediate in the synthetic route. After eight more additional steps the target molecule **2** is obtained in 11% overall yield.



Scheme XII.1 Synthesis of (–)-bitungolide F *via* an enantioselective organocatalyzed Michael addition.

A Michael addition procedure is also the organocatalytic step in the preparation of alkaloids dihydrocorynantheol [34,35,36], and protoemetinol [34,36] developed by Ma and co-workers (Scheme XII.2). The authors envisioned that intermediate **3** could be further transformed into different active alkaloids connecting it with a tryptamine, as the main core of final products.



Scheme XII.2 Syntheses of tryptamine derived alkaloids *via* an enantioselective organocatalyzed Michael addition.

XII.2.2 Dienamine Catalysis

A less explored mode of activation within aminocatalysis is the so-called dienamine catalysis [37]. In this case is an α,β-unsaturated carbonyl compound with a proton in γ position suitable of deprotonation that after condensation with a chiral amine provides a reactive nucleophile, but now two activated positions are available, being possible both α- and γ-funtionalization of the substrate. Additionally, this vinylogous enamine can also act as an electron-rich diene. The work published in this area is very scarce to date, and only few examples of its application in total synthesis came out in the last years: (+)-palitantin [38], α-tocopherol [39], pungent constituent of black cardamom [40], and (*R*)-rotundial [41] (Fig XII.3).

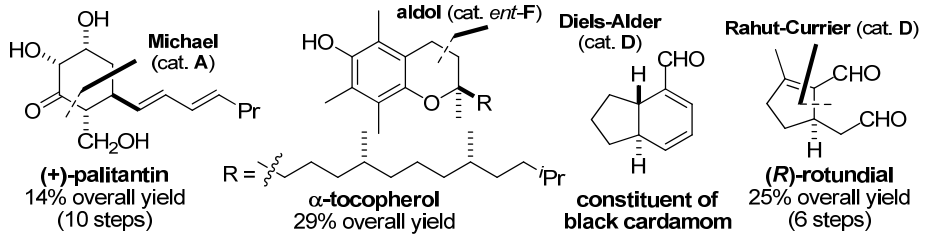


Figure XII.3 Natural products synthesized *via* dienamine catalysis.

XII.2.3 Iminium Catalysis

Aminocatalysis has been also successfully applied for the activation of α,β-unsaturated carbonyl compounds in order to conveniently activate the β-position through a reactive iminium ion, a more electrophile specie that the corresponding conjugated system [42]. The electron-deficient iminium intermediate can be further trapped by incoming electron-rich nucleophiles allowing the synthesis of final adducts with excellent levels of enantioselectivities. As well as enamine catalysis, iminium catalysis has been widely applied in natural product synthesis. Some representative applications of those syntheses employing this LUMO-lowering iminium catalysis as one of the key steps, are (+)-ricciocarpin A [43], (+)-fawcettimine [44], (*S*)-warfarin [45], (*S*)-rolipram [46], dysideaproline [47], INCB018424 [48], iriomoteolide 1b [49], psymberin [50], (+)-minfiensine [51], and diazonamide A [52] (Fig XII.4).

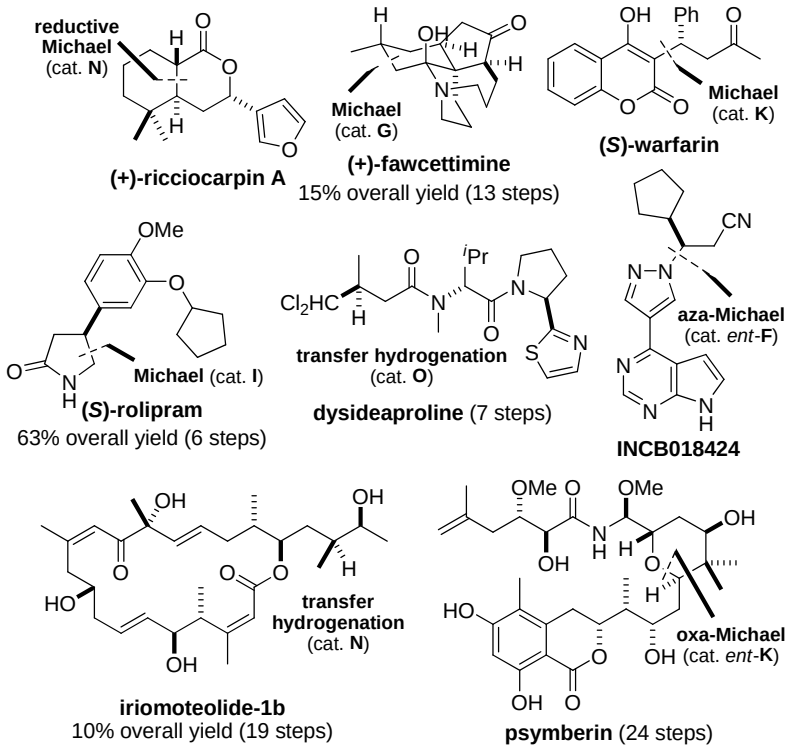
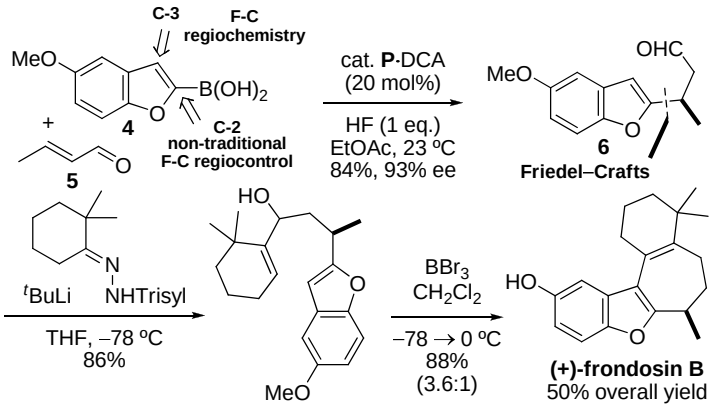


Figure XII.4 β-Funtionalization of carbonyl compounds *via* iminium catalysis applied in total synthesis.

MacMillan's group has worked intensively in the field of iminium catalysis, establishing a broad scope of applicability using this kind of activation and contributing actively to the development of this area. An elegant example is the three-step total synthesis of (+)-frondosin B in 50% overall yield [53], a member of a marine sesquiterpene family that exhibit significant properties in several therapeutic areas [54] (Scheme XII.3).

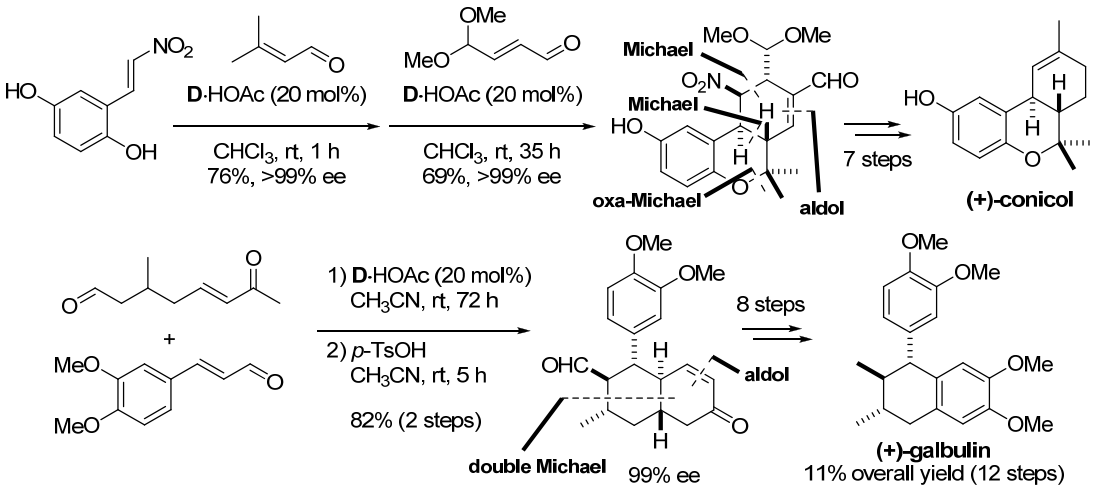


Scheme XII.3 Total synthesis of (+)-frondosin B *via* iminium organocatalyzed Friedel–Crafts reaction.

The key step of this synthetic route is an iminium organocatalyzed Friedel–Crafts reaction of an *in situ* generated activated boronate **4** intermediate and crotonaldehyde (**5**), forming a non-traditional Friedel–Crafts adduct **6**, result of an unexplored regioselectivity (C-2 *vs* C-3). Additionally, the feasible structural variations on the starting heteroaryl trifluoroborate salt could allow straightforward access to a variety of natural product analogues.

XII.2.4 Organocascade Catalysis: Combinations of Enamine and Iminium Catalysis[55]

In the last years, multicomponent [56] and domino [57] reactions have attracted the attention of a wide number of research groups due to the growing interest in atom economy and sustainable chemistry by the scientific community. Attractive achievements have been recently accomplished in the field of organocatalysis, being applied in the synthesis of important targets. Some extraordinary examples have been presented by MacMillan and co-workers. One is the synthesis of (–)-aromadendranediol *via* a Mukaiyama-Michael-aldol condensation, through a triple-catalysis-cycle-specific mechanism involving cross-metathesis, iminium and enamine catalysis [58]. And others more recent are the total syntheses of six well-known alkaloids (strychnine, aspidospermidine, vincadifformine, akuammicine, kopsanone and kopsinine) based on the combination of collective synthesis of natural products and organocascade catalysis [59]. Additional remarkable straightforward applications of organocascade catalysis have been published by Hong and co-workers. For instance, the first asymmetric total synthesis of (+)-conicol accomplished through an organocatalytic domino process oxa-Michael-Michael-Michael-aldol condensation, in a one-pot two-step reaction [60] is depicted in Scheme XII.4. Other interesting example is the synthesis of (+)-galbulin *via* an organocatalytic domino Michael–Michael–aldol condensation schematically represented in Scheme XII.4 [61].



Scheme XII.4 Total syntheses of (+)-conicol and (+)-galbulin *via* cascade organocatalytic reaction.

XII.3 Hydrogen Bond Catalysis in Total Synthesis

Catalysts acting by hydrogen bond interactions have significantly contributed to the progress of this area [62]. Among the great number of chiral acid catalysts recently developed and successfully applied as organocatalysts, chiral phosphoric acids and chiral (thio)urea have become two pivotal research areas in organocatalysis.

XII.3.1 Phosphoric Acids

Since pioneering works reported in 2004 by Terada[63] and Akiyama [64], chiral phosphoric acids have rapidly emerged as a new potent class of Brønsted acid catalysts with remarkable synthetic power owing to its continuous application in the development of new organocatalytic methodologies and resulting in a significant expansion of this field [65] (Fig XII.5). Proof of this substantial progress is the employment of such privileged class of Brønsted acids in the total syntheses of significant compounds as, for instance: (−)-arboricine A [66], (*S*)-anabasine [67], monastrol [68], (−)-zampanolide [69], (+)-galipinine [70,71], (+)-cuspareine [70], (−)-angusturine [70,72], and torcetrapib [73] (Fig XII.6).

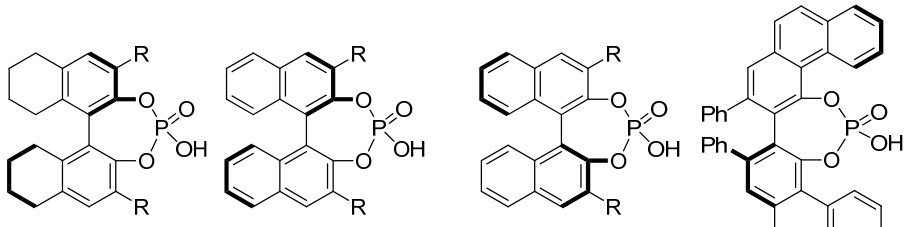


Figure XII.5 Chiral phosphoric acid derivatives utilized as organocatalysts.

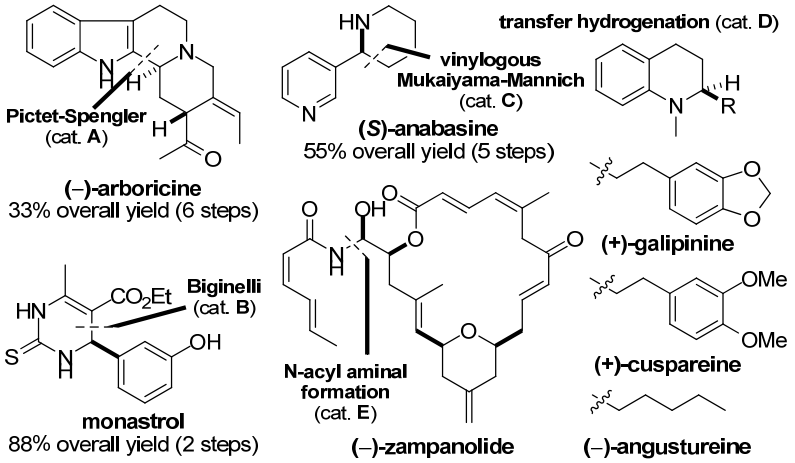
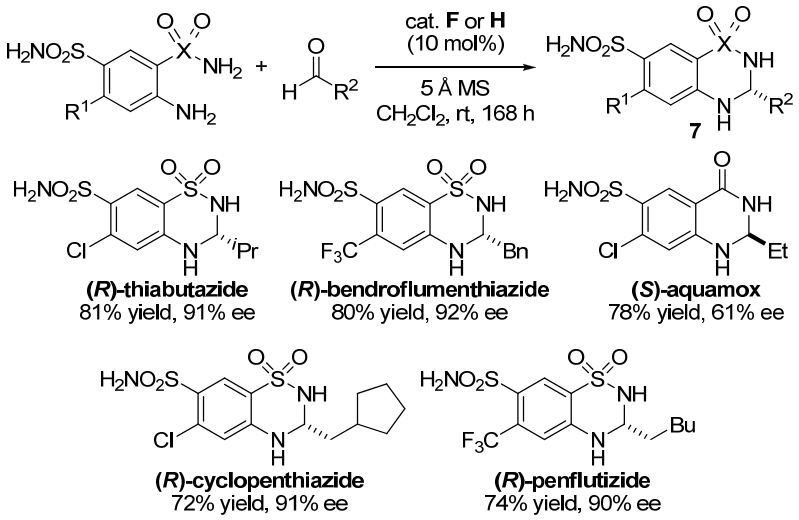


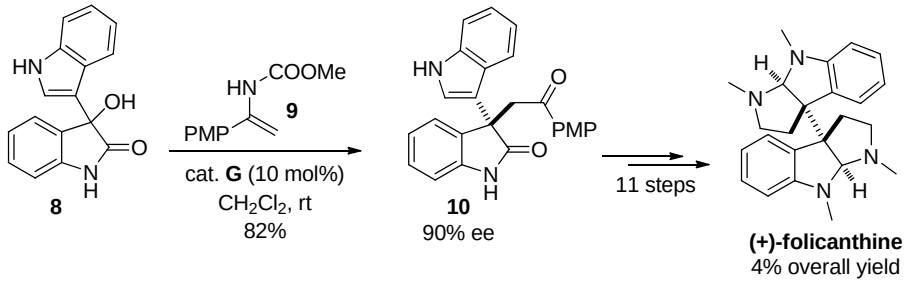
Figure XII.6 Brønsted acid catalyzed remarkable natural product syntheses.

List and co-workers published a practical and useful approach to chiral aminals **7** starting from aldehydes and employing chiral phosphoric acids as suitable catalysts. The authors applied this novel procedure in the straightforward synthesis of several benzo(thia)diazines pharmaceuticals, including (*S*)-aquamox, (*R*)-thiabutazide, (*R*)-penflutizide, (*R*)-bendroflumethiazide, and (*R*)-cyclopenthiazide with excellent enantioselectivities in one reaction step (Scheme XII.5) [74].



Scheme XII.5 Brønsted acid catalyzed synthesis of pharmaceutically relevant compounds.

More recently, a Brønsted acid organocatalyzed nucleophilic substitution reaction of 3-hydroxindoles **8** with ene-carbamates **9** was successfully developed by Gong's group for its application in the first catalytic enantioselective synthesis of (+)-folicanthine [75], member of the large cyclotryptamine alkaloid family which exhibit fascinating biological and pharmaceutical activities [76]. The 3,3'-disustituted oxindole intermediate **10** with a chiral quaternary stereogenic center is the key chiral building block in this synthetic route (Scheme XII.6).



Scheme XII.6 Total synthesis of (+)-folicanthine.

XII.3.2 (Thio)urea Organocatalyzed Processes

A different class of catalysts acting by hydrogen bond interactions covers the large group of (thio)urea derivatives (Fig XII.7). Although the application of this family of catalysts seems to be limited in comparison with Lewis acids due to their weaker hydrogen bonding, the concept of bifunctionality, by analogy with the catalytic action of some enzymes, has been extensively investigated in this area in order to increase their efficiency. In this context, intensive efforts have been devoted in studying the behavior of those structures as appropriate catalysts in a wide number of valuable organocatalytic processes [77]. Many of these chiral (thio)ureas have been already involved in the synthesis of remarkable molecules, such as (+)-esermethole [78], (+)-harmicine [79], (–)-CP-99,994 [80], (+)-yohimbine [81], (*R*)-(–)-calycotomine [82], (*S*)-(–)-salsolidine [82], (*S*)-(–)-carnegine [82], and (–)-epibatidine [83] (Fig XII.8).

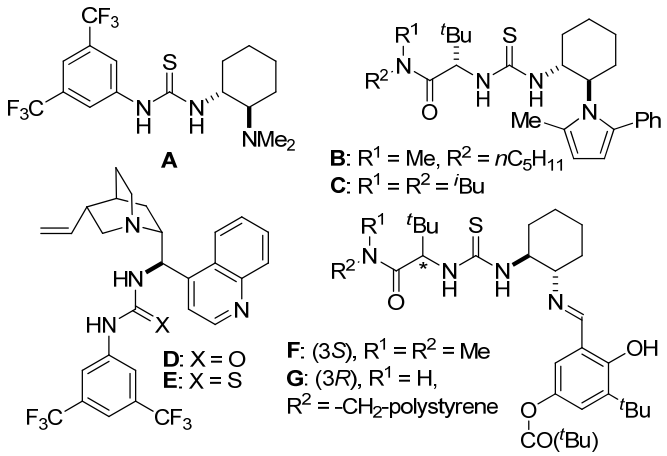


Figure XII.7 (Thio)ureas as organocatalysts in natural product synthesis.

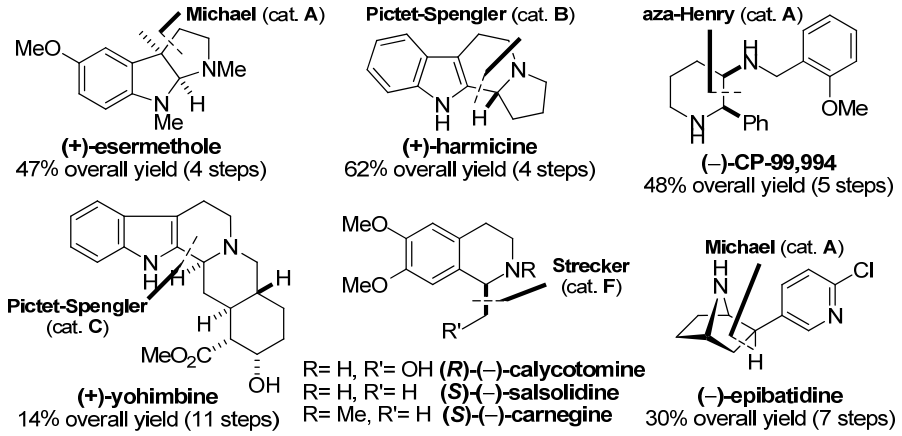
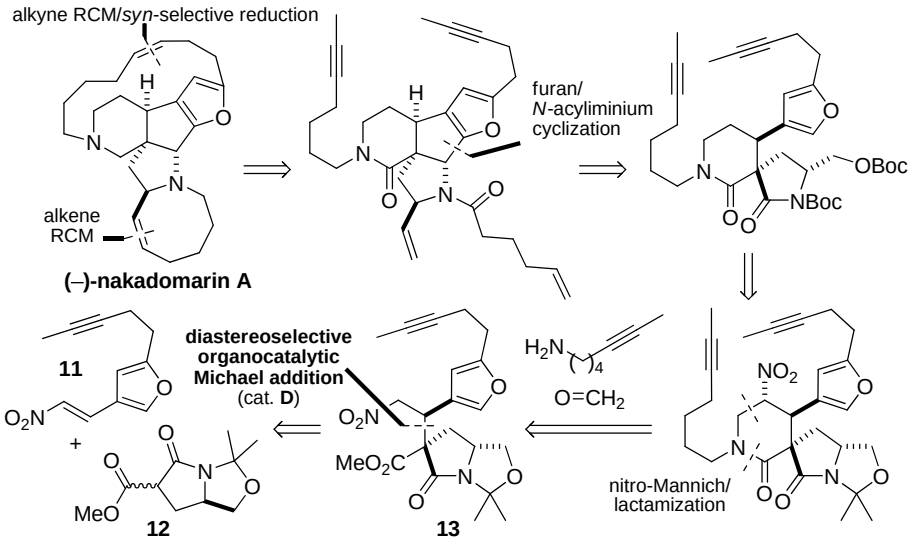


Figure XII.8 Significant total syntheses involving (thio)urea catalysts.

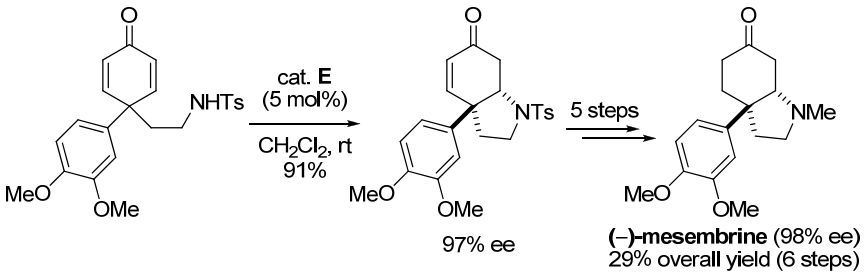
An elegant 19-steps synthesis of (–)-nakadomarin A has been reported by Dixon and co-workers (Scheme XII.7) [84]. It is a marine hexacyclic alkaloid which exhibits impressive biological activities [85], and a challenging complex structure for its total synthesis. A key step in this synthetic route is the diastereoselective organocatalyzed Michael addition between β-keto ester **12** and nitroalkene **11**. For high diastereoselectivity (dr 18:1:0:0) and short reaction time of this reaction, bifunctional urea **D** was required affording intermediate **13** as a single diastereomer in 81% yield after isolation.



Scheme XII.7 Retrosynthetic analysis of (–)-nakadomarin A.

Another example of the use of thiourea catalysts in total synthesis was reported by You and co-workers, where they obtained (–)-mesembrine by mean of an organocatalyzed aza-Michael addition process (Scheme XII.8) [86]. The crucial step in this route is based on a previous study about desymmetrization of cyclohexadienones performed by the same research group [87]. In this occasion, the difficult task of controlling the sterically congested chiral arylated quaternary

carbon center was reached by the use of bifunctional thiourea **E**, which facilitated the desymmetrization process [88] with high yield and enantioselectivity (91%, 97% ee).



Scheme XII.8 Enantioselective synthesis of (–)-mesembrine *via* desymmetrization of cyclohexadienones.

XII.4. Cinchona Alkaloids in Total Synthesis

Cinchona alkaloids, natural products extracted from *Cinchona officinalis*, have been extensively utilized in medicine as well as chiral ligands in metal catalysis [89]. Moreover, in the last decade these compounds have become powerful organocatalysts (Fig XII.9), used as Lewis or Brønsted base, and also acting as bifunctional catalysts in numerous examples [90]. Significant outcomes have been reached in this field, such as the total synthesis of pregabalin [91], (*S*)-baclofen [92], (+)-biotin [93], SNAP-7941 [94], (–)-mycestericin E [95], (+)-calanolide A [96], (+)-inophyllum B [96], DPP-4 inhibitor [97], mazacidin A and C [98], (+)-fostriecin and (+)-phoslactomycin B [99] (Fig XII.10).

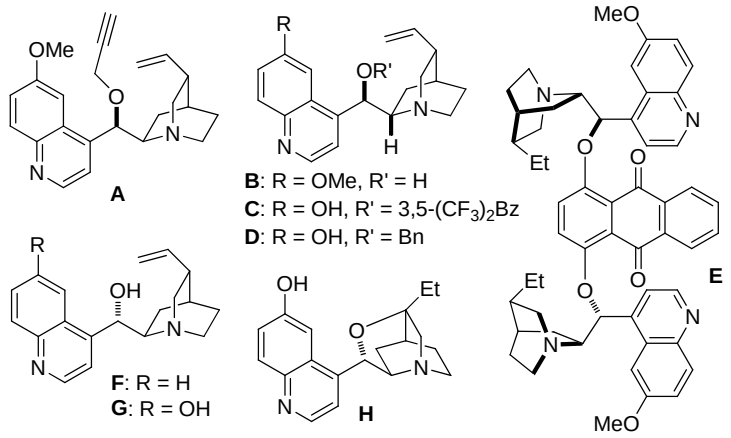


Figure XII.9 Efficient cinchona alkaloids as organocatalysts.

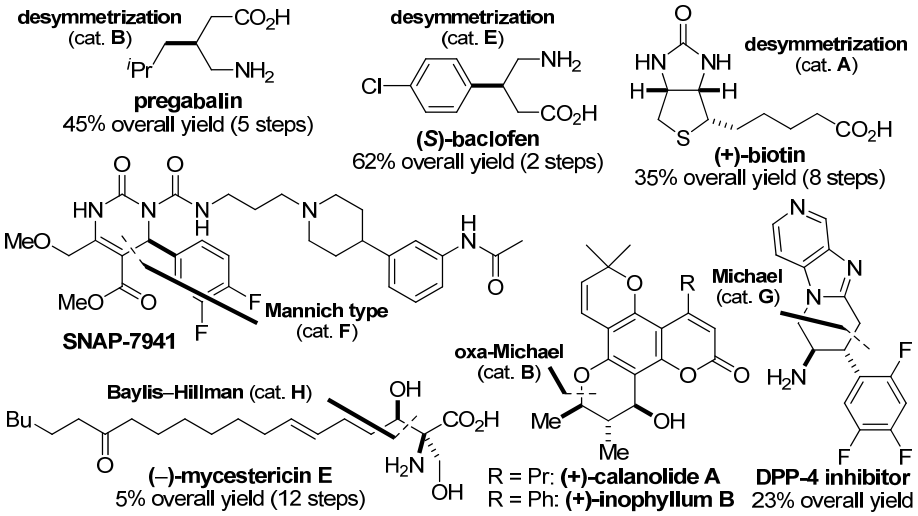
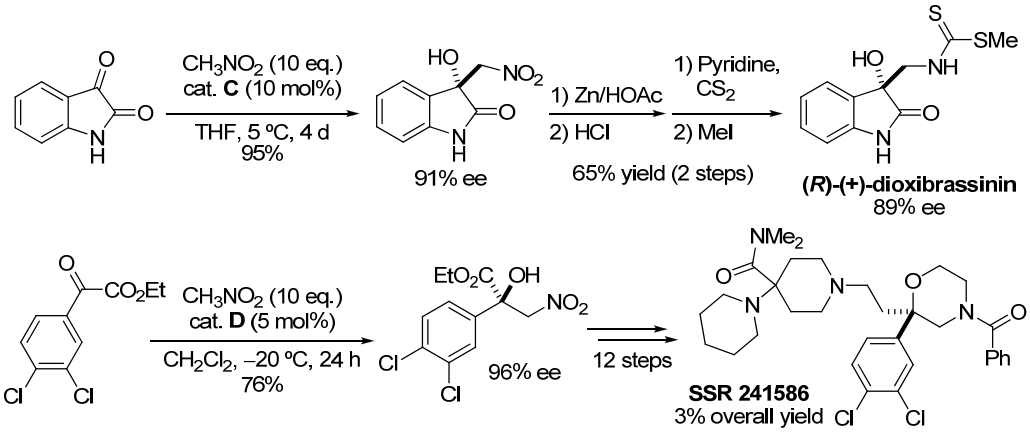


Figure XII.10 Target molecules synthetized using cinchona alkaloid organocatalysts.

In the following examples, using cinchona alkaloid catalysis, the key step of the syntheses is an asymmetric organocatalytic Henry reaction between a ketone and nitromethane. On the one hand, Wang's group published the total synthesis of (*R*)-(+)-dioxibrassinin as application of their method for the synthesis of chiral 3-hydroxy-2-oxindoles, that are important motifs in a variety of natural products and drugs [100] (Scheme XII.9). On the other hand, Gomez Pardo, Cossy and co-workers reported the synthesis of SSR 2415686 [101], an active drug in the treatment of schizophrenia and irritable bowel syndrome (Scheme XII.9). The construction of stereogenic quaternary centers is still an active and challenging task in organic chemistry [102]. In both strategies, ketones, as less explored substrates in organocatalytic Henry reaction [103], were used allowing the achievement of the required chiral quaternary centers with excellent enantioselectivities.



Scheme XII.9 Total syntheses of (*R*)-(+)-dioxibrassinin and SSR 241586 *via* organocatalyzed Henry reactions.

XII.5. Phase Transfer Catalysis in Target Molecule Synthesis

Although the term *phase transfer catalysis* was introduced in 1971 by Starks [104], this field has received especial attention in the last decades. The use of chiral ammonium salts as catalysts (Fig XII.11) have been recognized as an effective tool for organic synthesis and many efforts have been spent in both industrial and academic sectors, making possible to develop numerous highly enantioselective processes [105]. The applicability of PTC has been well demonstrated by the asymmetric synthesis of valuable active targets, such as (+)-cylindricine C [106], (+)-nemonapride [106,107], BIRT-377 [108], (+)- and (–)-methyl dihydrojasmonate [109], levobupivacaine [110], and ragaglitazar [111] (Fig XII.12).

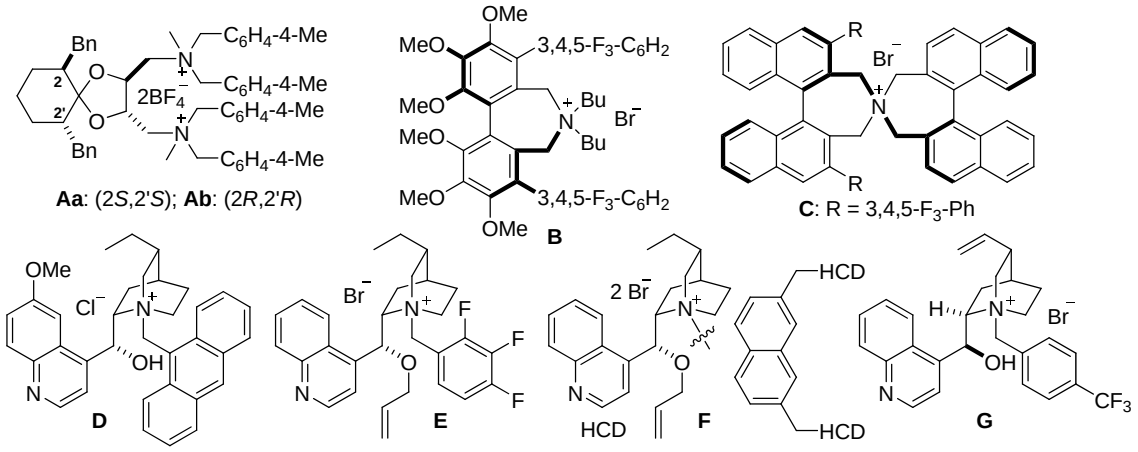


Figure XII.11 Model phase transfer catalyst structures.

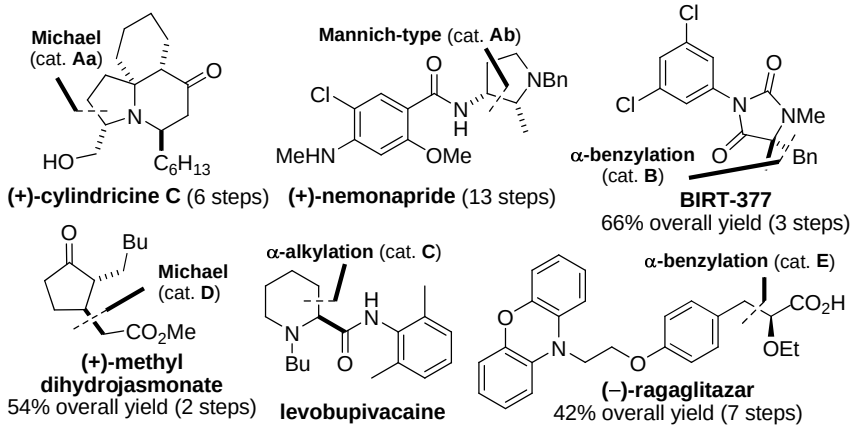
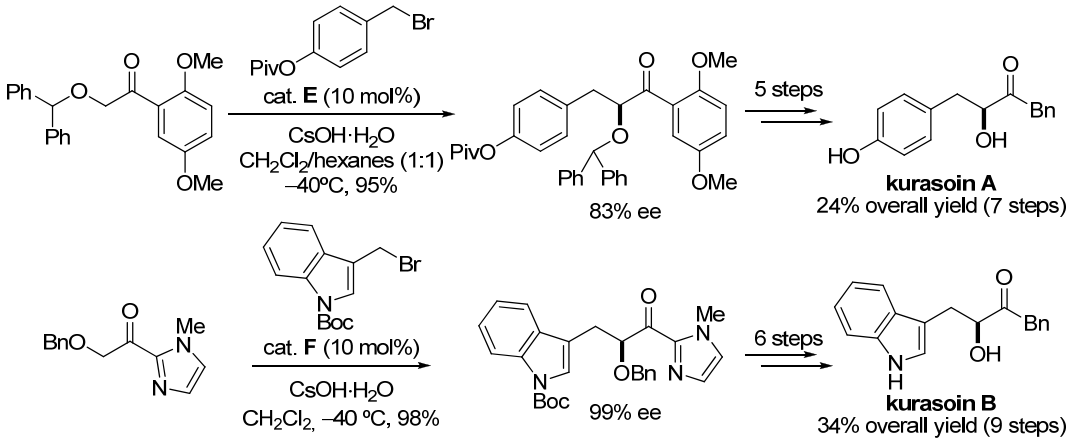


Figure XII.12 Appealing compounds synthesized by PTC.

The highly enantioselective syntheses of kurasoin A and B reported by Andrus and co-workers are illustrative examples of phase transfer catalysis utility. These compounds are protein farnesyltransferase (PFTase) inhibitors and were isolated for the first time from the fermentation broth of the soil fungus, *Paecilomyces* sp. [112], and due to their potential anti-cancer properties [113], a few groups have invested efforts in the development of new asymmetric total syntheses [114]. Andrus's research group firstly synthesized kurasoin A in seven-steps (24% overall yield)

through a phase-transfer catalyzed benzylation reaction to afford the central core of this PFTase inhibitor [115]. Later, the authors also applied a similar alkylation methodology to synthesize kurasoin B in nine-steps strategy (34% overall yield) (Scheme XII.10) [116].



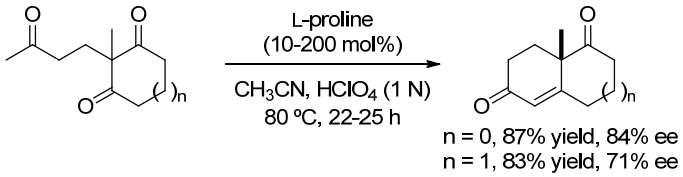
Scheme XII.10 Synthesis of kurasoin A and B by means of PTC.

XII.6 Industrial Applications of Organocatalysis

In the last four decades, the application of asymmetric catalysis in the industry has registered an increasing tendency, due to the importance of synthesizing chiral drugs in the pharmaceutical sector [117]. Despite its short history, few organocatalytic methodologies have also been successfully extrapolated to industrial applications. Nowadays, intensive efforts are invested increasingly in this direction, in order to scale-up organocatalytic procedures [118]. In this case, handling high amounts of catalyst could be easier and less toxic, since organocatalysts present some advantages respect to transition metal catalysts, such as their stability or recovery, and consequently becoming an attractive alternative and a suitable solution in the industrial sector. In this section, we briefly show to the reader some relevant industrial organocatalytic processes.

XII.6.1 Aminocatalysis at Industrial Sector

Most probably, the first and more significant industrial example of an asymmetric organocatalyzed process is the well-known Hajos-Parrish-Eder-Sauer-Wiechert reaction [119], independently discovered by two research groups in 1971 (Scheme XII.11) [120]. These two groups belonging to Schering and Hoffmann-La Roche industrial companies implemented this reaction since the early 1970s to manufacture steroids on multi-kilogram scales.



Scheme XII.11 L-Proline catalyzed Hajos-Parrish-Eder-Sauer-Wiechert annulation reaction.

This intramolecular aldol reaction has attracted attention from the beginning, for example due to the easy access to steroid precursors octahydronaphthalenedione **14** and tetrahydroindanone **15**, starting from readily available raw materials, and using commercially available L-proline catalyst (Fig XII.13) [121].

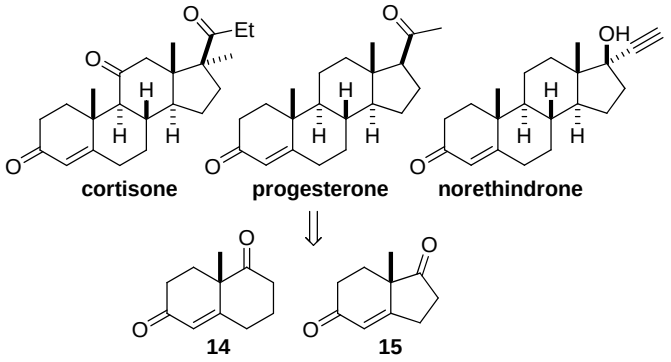
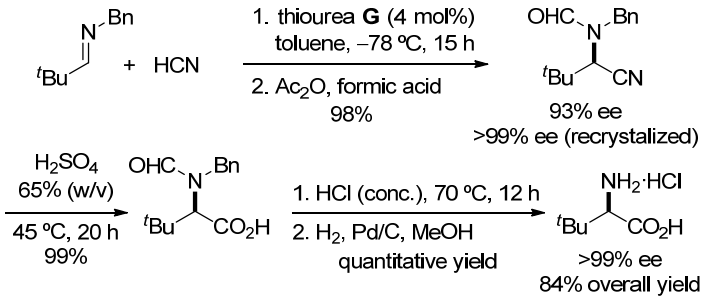


Figure XII.13 Relevant industrial commercialized steroids.

XII.6.2 Thiourea Catalysis at Industrial Scale

Another significant example utilized by commercially purpose is an asymmetric organocatalytic Strecker reaction [122], the most classical approach for the enantioselective preparation of α-amino acids. In this context, the methodology developed by Jacobsen and co-workers has been employed by Rhodia ChiRex for the large-scale synthesis of chiral amino nitriles **16** as useful building blocks for its further transformation in natural and unnatural amino acids (Scheme XII.12) [123]. The high efficiency of this process is demonstrated by the small amount of catalyst (4 mol%) necessary to provide final aminonitriles **16** in high yield and enantioselectivity.

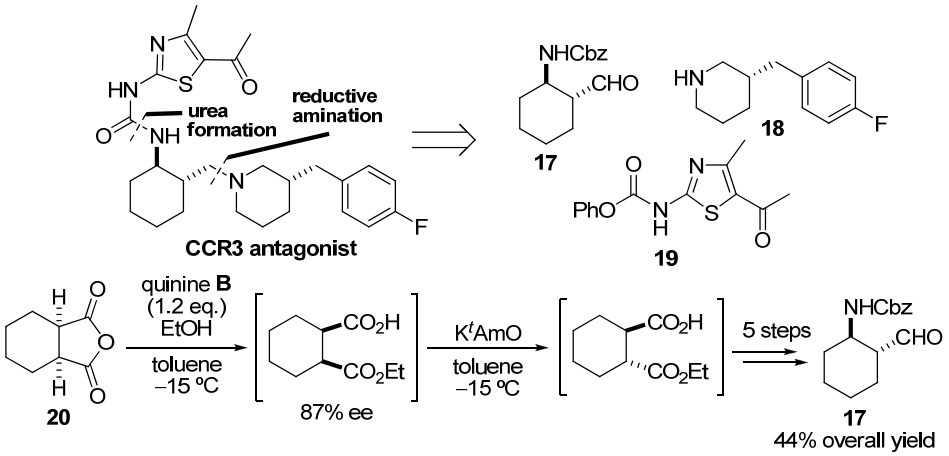


Scheme XII.12 Organocatalyzed synthesis of α-amino acids.

XII.6.3 Cinchona Alkaloids at Industrial Level

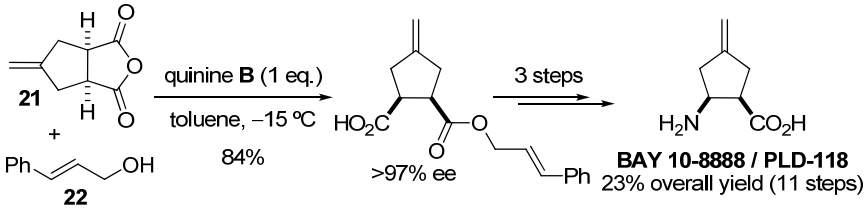
As above shown in part **XII.4** cinchona alkaloids have been used in several desymmetrization processes. In this field, Yue and co-workers have disclosed the stereoselective synthesis of a CCR3 antagonist, with potential activity in the prevention of inflammation in asthma and allergic rhinitis, in 20-kg pilot-plant manufacture [124]. The authors designed its synthesis from fragments **17-19**, through a reductive amination between fragment **17** and **18**, and urea

formation with fragment **19**. The synthetic route for preparation of the key fragment **17** starts from quinine-mediated opening of *meso*-hexahydrophthalic anhydride (**20**) with EtOH and involves seven steps with a 44% overall yield (Scheme XII.13).



Scheme XII.13 Retrosynthetic analysis of CCR3 antagonist, and synthesis of **17** through a desymmetrization reaction.

A desymmetrization step was also envisioned by a research group in Bayer AG to synthesize a new antifungal agent BAY 10-888 in multikilogram quantities in a pilot plant [125]. After screening different alcohols for the desymmetrization of the anhydride **21**, *trans*-cinnamyl alcohol (**22**) in the presence of stoichiometric amounts of quinine **B**, provided the best results suitable for carrying out the process on a pilot plant scale (Scheme XII.14).

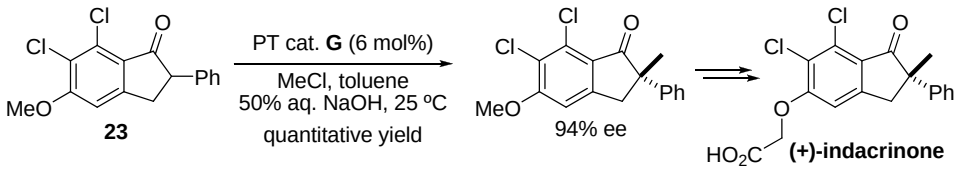


Scheme XII.14 Synthesis of BAY 10-888 through an organocatalytic desymmetrization reaction.

XII.6.4 Phase-transfer Catalysis in the Industry

Maybe one of the most employed organocatalysts at industrial scale are phase transfer catalysts. The first phase transfer catalyzed reaction carried out in the industry was developed by Merck Company in the mid-1980s [126]. The pioneering explored methodology was the methylation reaction of a cyclic ketone **23** in the presence of chiral ammonium salt **G** to create a chiral quaternary center. This process was developed with the objective of synthesizing (+)-indacrinone (MERCK-0197), a chiral indanone with diuretics properties and commercialized as uricosuric drug. The potential of this procedure is also reflected in economic aspects of the

production, since the catalytic process resulted less expensive than the obtainment of the active isomer by resolution from the corresponding racemate [126c] (Scheme XII.15).



Scheme XII.15 Enantioselective synthesis of (+)-indacrinone.

XII.7 Conclusions

In this work motivating applications of organocatalysis in the synthesis of relevant biological active compounds are presented. The most common organocatalytic approaches, such as aminocatalysis, hydrogen bond catalysis, cinchona alkaloids catalysts and phase transfer catalysis have been covered. We hope to give to the reader a general overview about the great utility of organocatalysis in total synthesis as well as at an industrial level. The examples highlighted here show that this kind of catalysis has become a powerful tool in the field of asymmetric oriented synthesis, being complementary to transition metal catalysis as well as enzymes. However, in spite of all these examples, organocatalysis is still in its infancy and there is still a long way to go. Although the role of the organocatalysts is still unclear in some cases, many efforts are focused in understanding the mechanism of the processes, which will allow overcoming several drawbacks like the need of high catalyst loadings and long reaction times. As a result, in the next future, we will assist to the development of new more complex examples of remarkable syntheses and its scaled-up for commercial applications is also expected.

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