Asymmetric Cu-catalyzed 1,2 and 1,4-additions of Grignard reagents

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Chapter 1: State of the art in steroid total synthesis

Introduction

The field of steroid synthesis has been a playground for chemists since its bloom in the 1930’s and 1940’s, due to their great potential as contraceptives and anti-inflammatory agents.¹ Benchmark total syntheses of steroids are the syntheses of estrone by the Torgov²,³ and the Vollhardt⁴ groups and the Woodward synthesis of cholesterol.⁵ A plethora of synthesis methodologies has been employed through the years in the synthesis of steroids, either to study their pharmacological properties, with the aim to produce steroid drugs on industrial scale, or to illustrate and test novel reactions. In particular carbon-carbon bond forming reactions using transition metal catalysis,⁶-⁷ pericyclic reactions⁸-⁹, and (organo-catalyzed) aldol cyclizations⁸, have been used. As steroids are chiral and contain quaternary stereocenters, stereoselectivity is at the heart of steroid total synthesis as well.¹⁰,¹¹ Due to the enormous number of literature reports, even when limited to total synthesis, we focus in this review on steroid syntheses reported from 2000 to 2015. Even with these constraints, we had to focus on reports dealing with the construction of the carbon skeleton.

Total syntheses of Estrone and Estrone derivatives

(+) - Estrone (1) (Figure 1) is an estrogen hormone found in the ovaries and in adipose tissue. It is responsible for the development and function of the female secondary sexual characteristics. Estrone was discovered and isolated by Adolf Butenandt, by its extraction from urine.

(B. C. Calvo and A. J. Minnaard; to be published).
Metal catalysis as the key step

In 2007, Knochel and co-workers published an enantioselective formal synthesis of (+)-estrone (1).\textsuperscript{12} Hydroboration followed by B/Zn exchange of Dane’s diene 2 afforded organozinc reagent 3 that underwent a copper(I)-mediated anti-S\textsubscript{N}2’-allylic substitution with enantiopure cyclopentene diol 4 to yield iodide 5 in 66% yield. Conversion of the iodide into the corresponding ketone 6 followed by acid catalysed ring closure, alcohol deprotection and oxidation to the ketone afforded Torgov’s diene 7. Conversion of the diene into (+)-estrone (1) had already been reported in 3 steps by Quinkert and Ogasawara.\textsuperscript{13,14}

Scheme 1: Knochel’s formal synthesis of (+)-estrone (1).

The Linclau group developed a strategy for the enantioselective synthesis of (+)-estrone via a C-ring closing metathesis and a B-ring Heck cyclization.\textsuperscript{15} From commercially available 3-methoxytoluene (8) 6 steps
lead to bromide 9, which can undergo diastereoselective conjugate addition followed by alkylation to furnish a 11 : 5 : 69 mixture of 10, 11 and 12, respectively. Compound 14 was obtained after ring-closing metathesis employing the Hoveyda-Grubbs 2nd generation catalyst (13). Heck reaction of bromide 14 furnished intermediate 15, which upon reduction of the double bond, or double bond isomerization followed by reduction, yielded a 3 : 7 mixture of products in favor of the desired estrone methylether (17), that was obtained pure after crystallization. Deprotection of the methyl ether gave (+)-estrone (1) in high yield (Scheme 2).

![Scheme 2: Linclau's strategy for the enantioselective synthesis of (+)-estrone (1).](image)

In 2011, Kotora and co-workers published a route to (−)-estrone (ent-1) in 12 steps from commercially available methoxytetralone (18).16 Introducing homochirality in the construction of the B ring, epoxide (19) was synthesized. This underwent Lewis acid catalyzed rearrangement to afford (−)-estrone methyl ether (ent-17) together with tertiary alcohol (20) (Scheme 3).
Scheme 3: Kotora’s synthesis of (−)-estrone methyl ether (ent-17). The group of Tietze developed a method for the enantioselective synthesis of (+)-estradiol (21) via multiple palladium-catalyzed transformations.\textsuperscript{17} Heck reaction of bromophenyl vinyl bromide (22) and the enantiopure indene 23 using Pd(OAc)$_2$ as catalyst led to (24) with excellent regio- and stereoselectivity. Subsequent intramolecular Heck reaction of (24) employing palladacene catalyst (25) furnished steroid intermediate (26) in excellent yield. The synthesis of estradiol (21) from (26) was subsequently accomplished in a few steps (Scheme 4).

Scheme 4: Tietze’s synthesis of estradiol (21).

Diels-Alder reactions as the key step
In 2004, Corey and co-workers published an enantioselective synthesis of (+)-estrone (1), whereas a few years later another enantioselective approach employing a CBS reduction as the key step was reported by the same laboratory. Enantioselectivity is introduced in the C ring via a Diels-Alder reaction employing a chiral oxazaborolidinium salt as the catalyst (27). The synthesis started with a Diels-Alder reaction between Dane’s diene (2) and dienophiles (28a) and (28b). Intermediates (29a) and (29b) were obtained in high yield and high enantiomeric excess (94% ee) that was improved to 100% ee by recrystallization. Treatment with 1 equivalent of MeMgBr afforded a γ-hydroxyester, which was subsequently reduced and then oxidized via Swern oxidation to furnish ketoesters (30a) and (30b). Base-catalyzed aldol cyclization followed by acid treatment provided Torgov’s diene (7) and diene (31). Finally, reduction of the double bonds and methylether deprotection yielded (+)-estrone (1) (Scheme 5).

Scheme 5: Corey’s enantioselective synthesis of (+)-estrone (1).

A few years later, Göbel and co-workers reported an enantioselective synthesis of (+)-estrone (1) via a hydrogen bond-promoted Diels-Alder reaction. Employing Dane’s diene (2) and methylcyclopentenedione (32), intermediate (33) could be synthesized in 91% total yield. The Diels-Alder reaction between (2) and (32) employing the amidinium catalyst (34) afforded the product in high yield and good enantioselectivity. Removal of
the hydroxyl group and double bond isomerization gave (35) in 99% ee after recrystallization. Torgov’s diene (7) was formed in good yield by reduction and posterior acid treatment. Stereoselective double bond reductions yielded (17) in 82% and final methyl ether deprotection followed by HPLC purification afforded (+)-estrone (1) in high yield and more than 99.9% ee (Scheme 6).

**Scheme 6:** Göbel’s hydrogen bond-promoted Diels-Alder approach to estrone.

Schotes and Mezzetti reported the use of dicationic ruthenium PNNP complexes (36) as catalysts in the asymmetric Diels-Alder reaction of unsaturated β-ketoesters. This approach was used in the synthesis of estrone precursor (37) reacting Dane’s diene (2) with dienophile (38), which successfully afforded the product in very good yield and good enantioselectivity (Scheme 7).
**Scheme 7**: Asymmetric Diels-Alder reaction catalysed by dicationic ruthenium PNNP complexes.

**Radical cyclization as the key step**

In 2004, Pattenden’s group developed novel cascade radical cyclizations that could be employed for the synthesis of rac-estrone (1). Starting with aldehyde (39), Horner-Wittig reaction followed by Heck arylation and Z-selective Wittig reaction afforded intermediate ester (40). Reduction of the ester functionality, cyclopropanation and again oxidation gave aldehyde (41). Grignard reaction followed by oxidation and Horner-Wittig reaction yielded (42) in 90%. TBAF deprotection and Appel reaction gave rise to iodide (43), which underwent a radical cascade cyclization to form (44). Lastly, Cr(VI) oxidation to the ketone and BBr₃ induced ether deprotection to furnish rac-estrone (1) in good yield (Scheme 8).
Scheme 8: rac-estrone (1) synthesis via a cascade radical cyclizations

Organocatalysis; Lewis acid-catalyzed cyclization

The List group published in 2014 a very elegant variation\textsuperscript{23} of Torgov's route,\textsuperscript{2} by making the acid-catalyzed cyclization step enantioselective with the use of a chiral Brønsted acid. Grignard addition to methoxytetralone (18) afforded tertiary allylic alcohol (49), which underwent base-catalyzed alkylation to give diketone (50). Here, enantioselection was induced in Torgov's cyclization by chiral disulfonimide (51), which furnished Torgov's diene (7) in 95% yield and 94% ee. Stereoselective double bond hydrogenation and subsequent methyl ether deprotection yielded (+)-estrone (1) in 75% (Scheme 9).
Scheme 9: List’s synthesis of (+)-estrone (1).

**Cholesterol and Desogestrel syntheses**

Cholesterol (52) (Figure 2) is an essential component of eukariotic cell membranes due to its regulatory function of their fluidity.

**Figure 2:** Cholesterol (52).

Rychnovsky’s laboratory developed a 16-step synthesis of ent-cholesterol (52) starting from commercially available (S)-citronellol (53) in 2% overall yield. Conversion of (53) into the corresponding α-diazo-β-ketoester (54) was achieved in good yield in 3 steps. Compound (54) underwent a diastereoselective C-H insertion employing the valine-derived phthalate ligand (55). The product was obtained in a 3.6 : 1 ratio in favour of the desired diastereomer, which upon column chromatography and recrystallization afforded the pure diastereomer (56) with 99% ee. Compound (56) could be transformed into ketone (57) after double bond
hydrogenation, alkylation and ester removal. Ketone (57) was converted into thio-ether (58) in 4 steps. Annulation of 58, with β-ketoester (59) provided enone (60) in 73% yield. Enone reduction followed by alkylation provided (61), which underwent acetal deprotection, aldol cyclization and finally selective reduction of the ketone with Li(OtBu)₃AlH to furnish ent-cholesterol (52) in 80% yield (Scheme 10).

**Scheme 10:** The synthesis of ent-cholesterol (52).

In 2004, in parallel with their enantioselective synthesis of estrone, Corey and co-workers published a modified synthesis of the third generation birth control compound desogestrel (67). Up to (31), the route is the same as previously described for estrone (1) (vide supra), with the exception that dienophile (28b) contains an ethyl instead of a methyl group. Acid catalyzed transposition of (31) gave (68). Following known procedures, intermediate (70) was synthesized and finally desogestrel (67) was obtained via their previous route (Scheme 11).
Scheme 11: Corey’s synthesis of desogestrel (67).

A few years later, Tietze’s laboratory reported on a synthesis of desogestrel (67) using double Heck arylations as the key steps.\textsuperscript{27} Alkene (72) is obtained in 3 steps from enone (71). Heck arylation between iodide (73) and (72) affords a 7:1.7:1 mixture of isomers in favour of desired (74). Purified bromide (74) could undergo intramolecular Heck arylation using palladacene (25) to successfully yield intermediate (75). Platinum catalysed double bond reduction of (75) and subsequent double bond isomerization produced (76). Alcohol (77) was made in 4 steps in 55% overall yield from (76). Dess-Martin oxidation followed by Peterson olefination yielded alkene (78) in 95%. Ether deprotection afforded (79) together with a minor isomer that could not be purified by means of recrystallization. Therefore, the mixture underwent another Dess-Martin oxidation and acetylene addition to form pure desogestrel (67) in 83% yield after column chromatography and recrystallization (Scheme 12).
Scheme 12: Tietze’s synthesis of desogestrel (67).

Other steroid-like compounds
Non-natural occurring steroid-type compounds

In 2006, it was reported by the Dyker group, that a suitable gold catalysed domino process leads to the synthesis of the steroid skeleton (Scheme 13). Alkyne (80), made in 3 steps from methylcyclopentadione, underwent a Sonogashira coupling followed by TMS deprotection to afford aldehyde (81) in very good yields. This intermediate was employed in a gold catalysed cyclisation, yielding (82), (83), and (84) in a 3:1:6 ratio. These could be unified via ester hydrolysis of (84) leading to (85) which, together with its diastereomer, was dehydrated to form diketone (82). Finally, hydrogenation and hydrogenolysis afforded partially reduced (86) and the racemic target compound (87) (Scheme 13). It is somewhat disappointing
that the keto function in the C-ring is removed in the final step, as functionalisation at this point is considered difficult.

**Scheme 13:** Steroid framework synthesis via a gold catalysed cyclization.

As well in the same year, the group of Kotora published a strategy based on the repetitive use of the Negishi reagent to obtain the steroid skeleton (93), (94) and (95) with cis-fused C and D rings (Scheme 14a).

The synthesis started with iodide (88), which after benzylation and Stille coupling afforded alkene (89). Oxidative addition of the benzyl ether to Cp₂ZrBu₂ and subsequent CuCl-catalyzed reaction with dichlorobutene afforded chloroallyl-ene (90), that was immediately converted into methoxy derivative (91). A second Cu-catalysed reaction with Cp₂ZrBu₂ and isobutenyl chloride led to (92). Treatment of (92) with Cp₂ZrBu₂ and CO afforded a mixture of cis-fused C and D rings steroids (93), (94) and (95). Compound (94) was converted into (95) upon reductive dehalogenation. An alternative route was employed to obtain trans-C,D-rings fused steroids (Scheme 14b). Starting from (96), bis-alkene (97) was obtained following the same route as for (92). Carbonylation of (97) under thermodynamic control afforded the C,D-trans-fused steroid (98), in low yield due to thermal decomposition.
Scheme 14: Kotora’s first strategy based on the repetitive use of the Negishi reagent.

Two years later the authors published an alternative route for the formal total synthesis of estrone (1). Based on the same strategy, but now performing a ring closing metathesis at the end of the synthesis to obtain intermediate (100), that could be converted into rac-estrone (1) according to previous literature (Scheme 15). Fluorine derivative (99) was employed in that case to favour the cyclization of the double bonds on the zirconium instead of the oxidative addition.
**Scheme 15:** Kotora’s second strategy based on the repetitive use of the Negishi reagent.

Another strategy based on an intramolecular alkylative arylation of an oxabicyclic alkene was envisioned for the synthesis of racemic estrone analogues. A Diels-Alder reaction between diene (101) and dienophile (102) gave oxabicycle (103). Reduction of the anhydride formed diol (104) which underwent acid catalyzed intramolecular alkylative arylation to form estrone analogues (105) and (106) in a 3:1 ratio, respectively (Scheme 16).

**Scheme 16:** Intramolecular alkylative arylation of an oxabicyclic alkene.

In 2008, Taber and Sheth reported on an efficient three-step route to a tricyclic steroid precursor. Wittig reaction of aldehyde (107) and phosphonium salt (108) gave alkenyl cyclopropane (109). UV irradiation of (109) in the presence of Fe(CO)$_5$ afforded 2-substituted cyclohexenone (110), that upon acid catalyzed cyclization delivered tricyclic steroid precursor (111) (Scheme 17).

**Scheme 17:** Synthesis of a tricyclic steroid precursor.

Kitagaki et al. reported the synthesis of estrone derivative (112) employing sequential pericyclic reactions of ene-dialenes. Starting from methylcyclopentenone (113), following a previously published procedure, rac-(114) was obtained. Protection via formation of a thioacetal and reduction of the ester group lead to (115), which was subsequently oxidised and underwent Wittig reaction to form aldehyde (116), coupled with (117) to afford (118), and deprotected to obtain diol
Finally, sequential pericyclic reaction of (119) afforded (112) after desulfoxidation (Scheme 18).

**Scheme 18:** Synthesis of estrone derivative (112) by sequential pericyclic reactions of ene-diallenes.

An interesting example of a route to “hybrid” steroids has been published by the group of De Groot applying Mukaiyama reactions. Two years later, this strategy was used by the same group in the development of new approaches towards the synthesis of (D-homo) steroids. The synthesis starts with carbocation formation of tertiary alcohol (49) with ZnBr₂. Reaction of TMS enolether (120) with this carbocation, gave (121) in good yield. As such, the silylenol ether is formed by conjugate addition to 2-methyl cyclopentenone followed by trapping of the (regioselectively formed!) enolate. Acid catalysed cyclization of (121) and stereoselective double bond reduction provided rac-(122) in 90% yield over the last two steps (Scheme 19). A strategy to carry out the conjugate addition in an enantioselective fashion has recently been disclosed.
Scheme 19: De Groot’s synthesis of steroid hybrid (122).

Chung and co-workers published in 2006 a route towards the basic steroid skeleton employing a Pauson-Khand reaction. Starting from commercially available β-tetralone, intermediate (123) could be made in a few steps. Intramolecular Pauson-Khand reaction of (123) followed by addition of NMO gave after 5 days steroid derivative (124) (Scheme 20). Although efficient, the product is just reminiscent of the steroid skeleton.

Scheme 20: A Pauson-Khand reaction in the construction of the steroid skeleton.

Another novel strategy to construct terpenes and steroids was developed by Tang and co-workers, in which the key step is an enantioselective palladium-catalyzed dearomative cyclization. Ketal (125) was reacted with bromide (126) to give (127) in a low 17% yield. Vinyl triflate formation and benzyl ether deprotection gave (128). This underwent palladium-catalyzed dearomative cyclization in presence of P-chiral biaryl monophosphine ligand (129) to afford product (130) in high yield and very good enantioselectivity (Scheme 21).

Scheme 21: Palladium-catalyzed dearomative cyclization by Tang et al.
Malacria’s group reported on the diastereoselective synthesis of \((rac)-(11)\)-aryl steroid skeletons via cobalt(I)-mediated \([2 + 2 + 2]\) cyclizations of allenediynes.\(^{41}\) \(trans\)-allene-diyn (132) was obtained in 2 steps from alkyne (131) Cyclization gave \(\eta^4\)-cobalt-complexed compound (133) in 60% yield as a single diastereomer, which was crystallized from a mixture of pentane/DCM. Finally, treatment of (133) with silica gel gave free (134) in 90% yield (Scheme 22).

**Scheme 22:** Cobalt(I)-mediated \([2 + 2 + 2]\) cyclization of allenediynes.

Lu and Ma reported on a Rh-catalyzed triple allene approach for the stepwise synthesis of steroid-like tetracyclic skeletons.\(^{42}\) \(trans\)-RhCl(CO)(PPh\(_3\))\(_2\)-catalyzed cyclization of 1,5-bisallene (135) and monoallene (136) in toluene provided (137) in a moderate yield. Allylation and Diels-Alder reaction of (137) and dienophile (138) furnished tetracyclic compound (139) in good yield and diastereoselectivity. Compound (140) could be synthesized in 3 steps from (137) (Scheme 23).

**Scheme 23:** A Rh-catalyzed triple allene approach to the steroid skeleton.

Süninemann and de Meijere developed a strategy towards steroids and steroid-like molecules employing Stille coupling – Heck reaction
sequences. Bromides (142) and (143), obtained in 4 steps (including a Stille coupling) from enone (141), underwent Heck reaction to furnish (144) and (145) in good yields. Heating in decalin yielded the cyclized products (146) and (147) in 71-75% (Scheme 24). This is an interesting route since it provides unnatural cis-regular-ring fused steroids.

**Scheme 24:** Steroids and steroid analogues by Stille coupling – Heck reaction sequences.

Another elegant route from de Meijere and co-workers, leading to a great variety of steroids, was to combine Stille coupling and Diels-Alder reaction. Preparing diene (148) via a Stille coupling, this could subsequently undergo different high yielding Diels-Alder reactions to afford steroid derivatives (Scheme 25).

Gagné’s laboratory published a biomimetic steroid synthesis based on an alkene-terminated cation-olefin cascade reaction. This is initiated by the dicationic platinum complex (PPP)PtI$_2$ (PPP = bis-(2-diphenylphosphanylethyl)phenylphosphane). The use of a polar solvent (EtNO$_2$) together with Ph$_2$NMe or a resin bound piperidine base afforded successfully the cyclization of the trienes (149), (150) and (151) to yield (152), (153) and (154) in 89-97% (Scheme 26).
Scheme 26: Platinum-catalyzed cyclisation reactions

Nörret and Sherburn developed a strategy for the synthesis of tetracycles reminiscent to the steroid skeleton. Employing a domino intramolecular Diels-Alder reaction (IMDA), the tetracycles could be obtained in a single step in a stereoselective fashion. The domino IMDA precursor (156) was obtained in 6 steps from aldehyde (155). IMDA reaction afforded three stereoisomers; the cis-fused C/D ring system in (157) and (158), resulting from an endo-docking mode, and the trans-fused C/D moiety in (159) from a minor exo-pathway (Scheme 27).

Scheme 27: Domino IMDA cyclization in the synthesis of steroid-like compounds.

Heterocyclic steroids:

The synthesis of heteroatom containing steroids is an interesting field due to the unknown properties of these non-natural steroids. The group of Otto published several syntheses of azasteroids based on Diels-Alder
reactions. The combination of Dane’s diene analogue (160) and maleimide (161) yielded TMSO-substituted azasteroids (162) and (163) in a 87 : 13 ratio, respectively. Acid catalyzed hydrolysis afforded azasteroids in very good yield (Scheme 28).

Scheme 28: Otto’s azasteroid synthesis.

Ibrahim-Ouali et al. published on the synthesis of aza-thia, aza-seleno and aza-telluro steroids prepared via intramolecular Diels-Alder reaction. Intermediates (1659 and (166) were obtained in 3 steps from so-called BISTRO (164) and chloroacetic anhydride. These compounds underwent alkylation with iodides (167) and (168) to generate the corresponding aza-thio and aza-seleno intermediates in moderate yields. Finally, intramolecular Diels-Alder reaction of afforded 5 : 1 and 9 : 1 mixtures of the corresponding heterocyclic steroids in favour of the all-trans-fused ones (Scheme 29).

Scheme 29: Synthesis of aza-thio and aza-seleno steroids.

An elegant extension of this strategy for the synthesis of more than 250 unnatural steroids was recently reported by the Santelli group. Starting with BISTRO (164), which was obtained via reductive dimerization of buta-
1,3-diene in presence of TMSCl, 1,1-disubstituted 2,5-divinylcyclopentanes could be obtained via reaction with various electrophiles e.g. anhydrides and 1,2-diones. The 2,5-divinylcyclopentanes could be coupled with cyclobutenes. Heat-induced ring opening of the benzocyclobutenes and subsequent intramolecular cycloaddition with a vinyl substituent forms the steroid skeletons (169), in overall yields exceeding 25% (Scheme 30).

Scheme 30: The BISTRO-strategy for the synthesis of unnatural steroids.

Natural occurring steroids

In 2008, the Sherburn group reported the formal total synthesis of triptolide (170), an anti-tumour and anti-inflammatory natural product isolated for the first time in 1972 from the Asian vine Tripterygium wilfordii. The key steps in this synthesis are two Diels–Alder reactions and a new deoxygenative aromatisation reaction. Two Diels-Alder reactions between (171), (172) and (173) formed (174), that could be transformed into (175). Triptolide was obtained in 8 subsequent steps from (175) (Scheme 31).

Scheme 31: Sherburn’s formal synthesis of triptolide (170).

In 2000, Stoltz, Kano, and Corey published the enantioselective synthesis of the nicandrenones, a family of steroid-derived natural products with insect repellent and antifeedant properties. Exo-selective Diels-Alder reaction between diene (176) and dienophile (177) provided the
tetracyclic compound (178). In 16 steps from (178), (179) was obtained. Stille coupling with vinylstannane (180) furnished (181), which upon reduction and epoxidation, formed (182). Conversion into epoxylactone (183) was achieved in 90% yield over two steps. (262) was obtained from (261) by replacement of the Me₂PhSi group by a hydroxyl function and β-elimination by acetylation followed by treatment with DBU. Finally, reduction of both carbonyls, selective acetylation of the more reactive lactol hydroxyl, Dess-Martin oxidation, and deacetylation furnished nicandrenone (185) (Scheme 32).

**Scheme 32:** Corey’s group synthesis of the nicandrenones.

Jung and Yoo published in 2011 the first total synthesis of the cardiac glycoside rhodixin A (186),⁵⁶ which had been isolated in 1951⁵⁷ from the Japanese evergreen Rhodea japonica. Silyl-protected enynone (187) underwent metathesis reaction with Grubbs 1st generation catalyst to afford diene (188). Inverse-electron-demand Diels-Alder reaction between (188) and vinyl silylenol ether 189 yielded the adduct in 87% forming 4 contiguous stereocenters in 1 step. Dihydroxylation and protection of the diol was accomplished to give (190), which could be transformed into (191) in several steps. Cross metathesis followed by cyclization furnished (192) in good yield. In seven additional steps (193) could be obtained.
Hydrolysis of the TBS ether and subsequent reaction with the Bestmann reagent formed the butenolide in 70% yield. Selective removal of the C-3 acetate, in the presence of the C-11 acetate, employing HCl in methanol gave diol (194) in good yield. Finally, glycosidation and deprotection provided rhodixin A (186) (Scheme 33).

Scheme 33: The first synthesis of rhodixin A (186) by Jung and Yoo.

Conclusion

This review compiles the recent developments in the field of steroid total synthesis from 2000 on. Many different approaches have been employed, transition metal catalysis as well as Diels-Alder and other pericyclic reactions reaction being dominant. As for the latter, this is not surprizing, as these are the strategies par excellence to form cyclic compounds. Nevertheless, organocatalysis, more precise asymmetric organocatalysis is an important novel approach, and in need, as many of the reported syntheses reported earlier are racemic. In general one can state that several steroid skeletons and a series of closely related derivatives are now readily available by total synthesis. Where steroid synthesis was once considered equivalent with lengthy synthesis routes, this is no longer the case. However, even slight deviations in carbon skeleton and substitution pattern can change this picture and add a series of additional
transformations. As the production of the steroids used in medicine has been optimized and streamlined for years, there is currently limited interest of the pharmaceutical industry in novel steroid synthesis. In chemical biology, however, interest in steroids and steroid-derivatives is increasing as steroids play important and multifaceted roles. Contrary to lipids, that are difficult to label without disturbing their structure, steroids can be labelled and their fate in the cell can be studied with spectroscopic techniques.

In this thesis, we will show our approach to the enantioselective synthesis of steroids derivatives. Therefore, we considered that a review of the current state of art in steroids synthesis would be an interesting addition to the topic. In further chapters, methodology to perform enantioselective Cu-catalyzed 1,4 and 1,2-additions will be investigated. And finally, the application of this methodology to the steroid synthesis will be shown.
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