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Organocatalyzed Asymmetric Friedel–Crafts Reactions

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Aromatic substitution enables the synthesis of relevant and promising biological entities through the direct synthesis of a range of highly functionalized compounds. Thus, since its discovery and over more than one century, the Friedel–Crafts (F-C) alkylation has been used for carrying out such a transformation. Despite its aptitude and viability for aromatic substitutions, it is quite surprisingly that catalytic and asymmetric versions of F-C reactions have only been described in the mid-1980s. In this microreview, we are planning to underscore the main and recent developments in organocatalyzed F-C reactions which were published within the 2001–2009 timeframe.

1. Introduction

Through the years, the discovery of new chemical transformations allowing efficient and practical syntheses of complex structures has been the main objective for synthetic organic chemists in industry and academia. For this purpose, a plethora of organic reactions that allow the stereocontrolled synthesis of important scaffolds via Carbon–Carbon and Carbon–Nitrogen bonds from available starting materials has emerged. The Friedel–Crafts (F-C) alkylation,[1] one of the oldest organic synthetic methods, is still one of the most powerful and employed reactions that enable such transformations and has been widely used to generate important classes of building blocks. Al-

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Vincent Terrasson was born in Toulon-France in 1981. After studies at the Ecole Nationale Supérieure de Chimie de Rennes, he received his Ph.D in 2008 under the supervision of Pr. D. Prim at the University of Versailles on the synthesis of heterocyclic vicinal diamines and their application as ligands for transition metal catalysis (Pd, Cu). He is currently pursuing postdoctoral research at the Ecole Nationale Supérieur de Chimie de Montpellier in the group of Prof. J. M. Campagne on the development of new asymmetric organocatalyzed reactions.

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Jean Marc Campagne was born in Pau, France, in 1967. After studies at the Ecole Nationale Supérieure de Chimie de Montpellier, he received his Ph.D. at the University of Montpellier in 1994. After post-doctoral training with Prof. B. Trost (Stanford University, USA) and Prof. L. Ghosez (Université Catholique de Louvain, Belgium), he was appointed CNRS researcher at the Institut de Chimie des Substances Naturelles in Gif-sur-Yvette in 1998. Since 2005 he moved to the Ecole Nationale Supérieure de Chimie de Montpellier where he was appointed as professor. His current interests concern the development of catalytic asymmetric transformations and their application to the total synthesis of natural products.

though F-C reaction has proven its relevancy since its discovery in 1877,[2] first asymmetric and catalytic versions of this methodology have only started being reported during the last decade.[3] Indeed, the first examples of catalytic and asymmetric F-C alkylation appeared in the middle of 80s.[4] Since then, many groups have directed their efforts in developing new routes to devise efficient and adapted strategies for this purpose.[3] While the first examples of catalytic and asymmetric F-C alkylations have been described via metal-catalyzed addition of aromatic substrates to electron deficient σ-(epoxide opening) and π-systems (1,2 carbonyl and 1,4 conjugate additions), nowadays, the field of organocatalysis[5] has paved the way to the discovery of new asymmetric protocols for guiding such relevant transformations.[6]

This microreview covers the literature related to the construction of highly functionalized enantiomerically enriched entities in the context of the organocatalyzed F-C reactions. Since the first report came out in 2001, an increasing interest on this topic has allowed to the publication of a high number of methods and the main publications have been described in the last three years showing its growing impact. It is not intended to give an exhaustive account, but rather highlight recent advances on imidazolidinone, cinchona alkaloids, diarylprolinol derivatives, phosphoric acids and thioureas mediated organocatalyzed F-C transformations.

2. Imidazolidinones

At the beginning of the 21st century, benzyl imidazolidinones·HX salts derived from (*S*)-phenylalanine have been sophisticatedly tailored by MacMillan's group in order to achieve crucial asymmetric transformations from which important entities for organic chemistry arise in very good yields and excellent selectivities (Figure 1).[7,8] Since then, such small organic molecules have been widely employed and, to date, they are still proving their catalytic power avoiding the need of metal catalysts that are commonly more expensive, less stable, operationally complex and environmentally unfriendly.

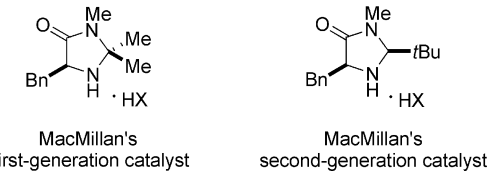
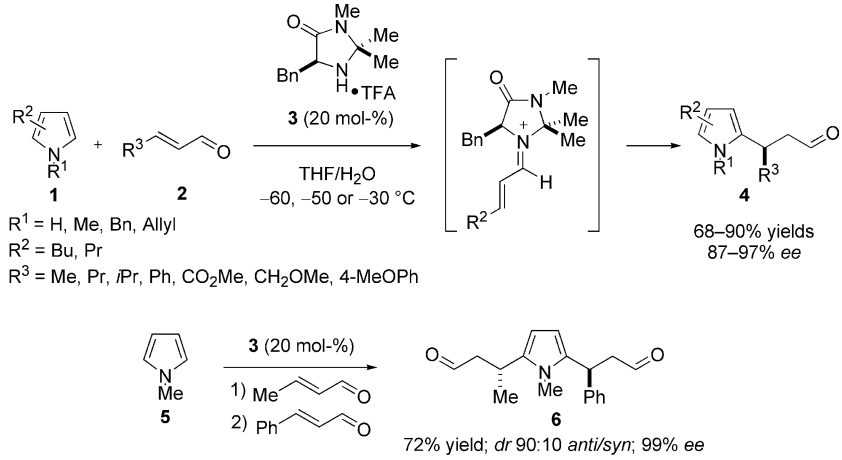


Figure 1. MacMillan's chiral benzyl imidazolidinone organocatalysts.

Along with their utilization for enantioselective organocatalytic Diels–Alder reaction[7] and 1,3-dipolar cycloaddition,[8] pioneering work in the field of organocatalytic F-C reaction was devised by MacMillan et al. in 2001 (Scheme 1).[9] They used their strategy based on the LUMO-lowering activation of α,β-unsaturated aldehydes via the reversible formation of iminium ions with chiral imidazolidinone which is responsible for the stereo-outcome and reactivity of the transformation. By computational studies, they anticipated that steric constraints imposed by the catalyst structure could avoid the more commonly 1,2-carbonyl addition (that is observed when acid catalysts are used) in profit of the less sterically demanding 1,4-addition. Thus the F-C alkylation of different *N*-alkyl pyrroles takes place at lower temperatures (–30 to –60 °C) with 20 mol-% of the catalyst salt **3** giving rise to β-pyrrolyl carbonyls **4** in good yields (68–90%) and enantioselectivities (up to 97% *ee*) (Scheme 1). Unsaturated aldehydes containing bulky, aromatic or even electron-deficient groups that do not facilitate the iminium formation are tolerated. Notably, double F-C alkylation starting from the pyrrole **5** was observed and a non symmetrical disubstituted pyrrole derivative **6** was isolated in 99% *ee* (*dr* 90:10 *anti*, 72% yield over 2 steps).

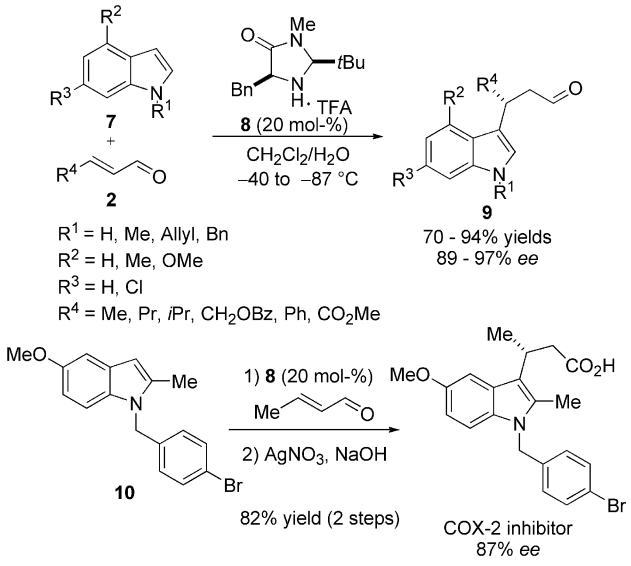
In the same year, MacMillan et al. have also devised an enantioselective organocatalytic indole[10] alkylation (Scheme 2).[11] In this case, catalyst **8** has shown improved efficiency for iminium formation compared to **3** and, consequently, better reactivity toward carbon–carbon bond formation. Indole alkylations occur at lower temperatures (–40 to –87 °C) with 20 mol-% of catalyst loading. This



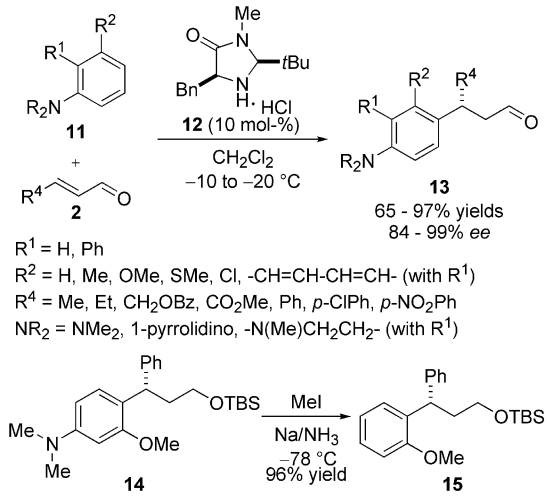
Scheme 1.

imidazolidinone-catalyzed transformation is general with a wide range of aldehydes (e.g. electron-deficient, steric encumbered and aromatic) as well as with modifications in the indole architecture. The desired alkylated indoles **9** were obtained in very good yields (70–94%) and excellent enantioselectivities (up to 97% *ee*). A practical synthetic application of this organocatalyzed method was the preparation of indolobutyric acid, a COX-2 inhibitor (82% yield, 87% *ee* over 2 steps).[12]

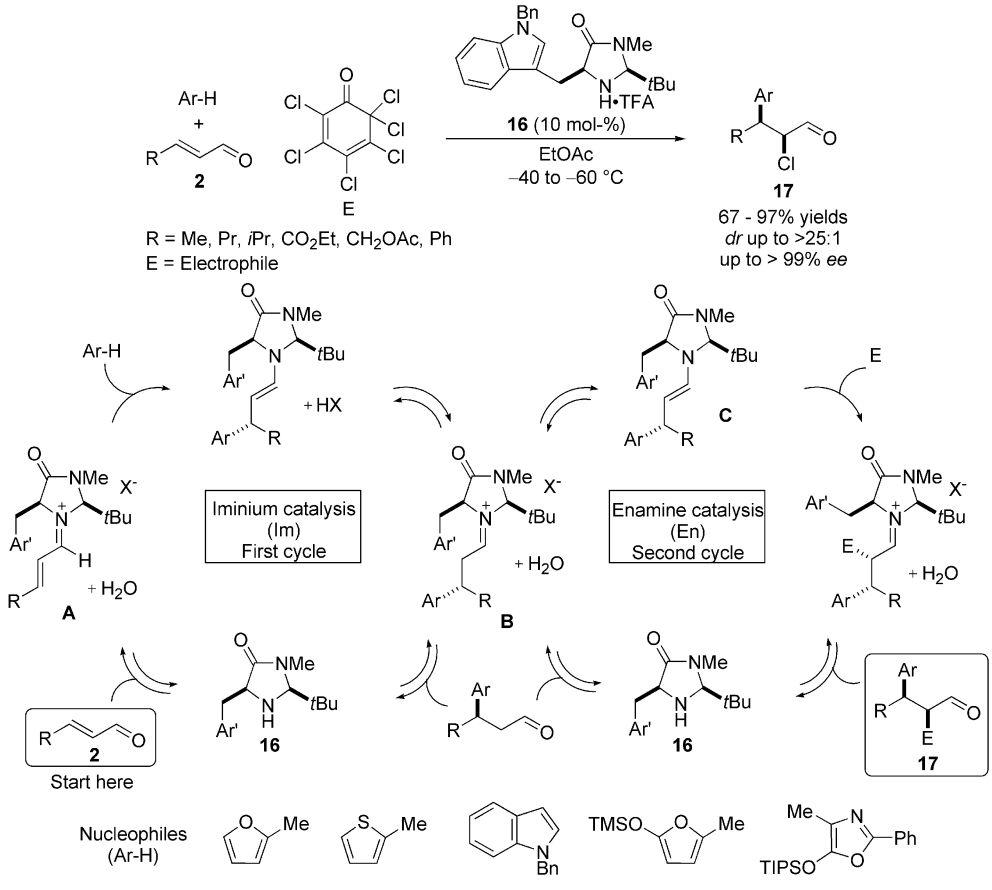
The powerful MacMillan's method for enantioselective F-C alkylation of indoles and pyrroles via iminium catalysis has also been extended to aniline rings (Scheme 3).[13] In the presence of 10 mol-% of catalyst **12** at subambient temperatures (–10 to –20 °C), the addition of anilines deriva-



Scheme 2.



Scheme 3.

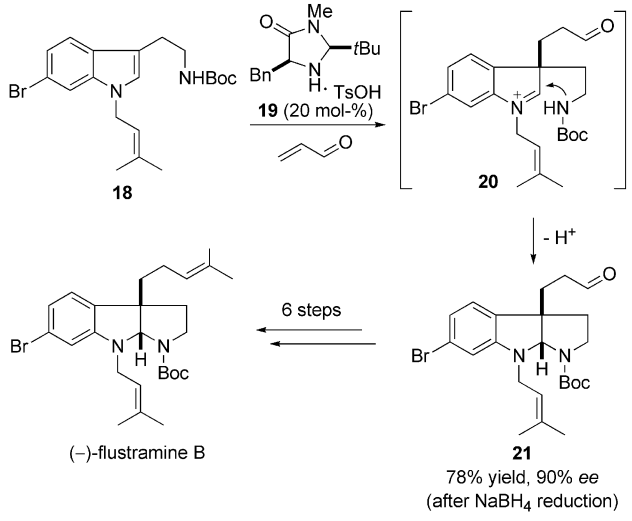


Scheme 4.

tives **11** to a broad range of aldehydes **2** occurs in very good yields (65–97%) and remarkable enantioselectivities (up to 99% *ee*). The catalyst loading can be decreased from 10 to only 1 mol-% without losing the reaction efficiency. It is important to point out that the products here obtained can be easily transformed into their parents' benzene systems by simple exposure of the quaternary amine (resulted from the reaction with MeI) followed by reductive conditions (Na/NH_3).

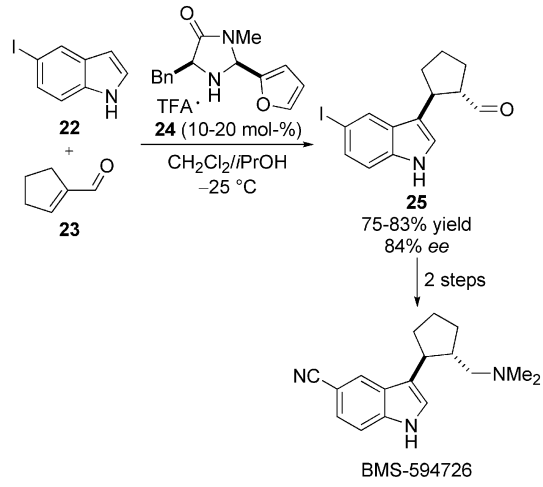
Three years later, iminium-enamine activation has been used by the same group in order to accomplish an enantioselective organo-cascade transformation (Scheme 4).[14] Via a F-C alkylation over the iminium species **A** followed by the trapping of the resulting enamine intermediate **C** (obtained after hydrolysis of iminium **B**) with the chlorinated quinone E, complex molecular entities were isolated in very good yields (67–97%) and excellent selectivies (*dr* up to >25:1 and up to >99% *ee*). According to their observations, the high level of diastereoinduction seems to be directed by the catalyst structure and not by the chiral center created in the first catalytic cycle (F-C alkylation).

In a synthesis of the alkaloid flustramine B,[15] a F-C alkylation of the 6-bromotryptamine derivative **18** with acrolein in the presence of 20 mol-% of catalyst **19** gave rise to intermediate indolium ion **20** which was readily intercepted by the Boc-amino group to afford intermediate **21**. Six additional steps allowed to the synthesis of (–)-flustramine B in a very elegant manner (Scheme 5).



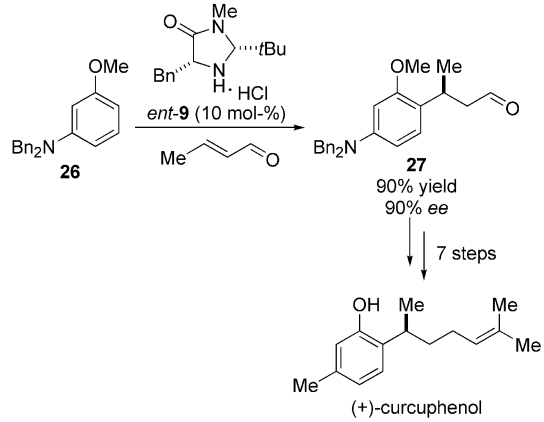
Scheme 5.

King, Meng et al. employed a F-C alkylation of indole and the α-branched aldehyde **23** in order to devise a concise and very efficient synthesis of the selective serotonin reuptake inhibitor BMS-594726 (Scheme 6).[16] In this case, at –25 °C catalyst **24** (10–20 mol-%) showed better efficacy and aldehyde **25** was isolated in 75–83% yield (84% *ee*). The synthesis was completed via reductive amination of **25** followed by cyanation (80–83% yield).



Scheme 6.

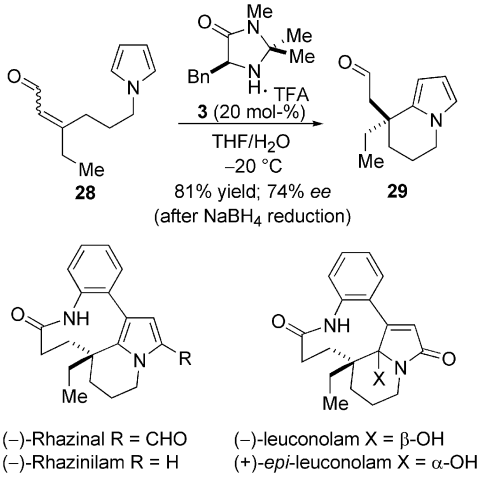
An elegant synthesis of (+)-curcuphenol involved imidazolidinone catalysis as a key step by Kim et al.[17] They used F-C alkylation of *N*,*N*-dibenzyl-3-anisidine (**26**) with crotonaldehyde in the presence of 10 mol-% of catalyst *ent*-**9** in order to prepare the intermediate **27**. After 7 steps, (+)-curcuphenol, a bioactive sesquiterpene phenol with antifungal, antitumor and antimalarial activity was isolated (Scheme 7).



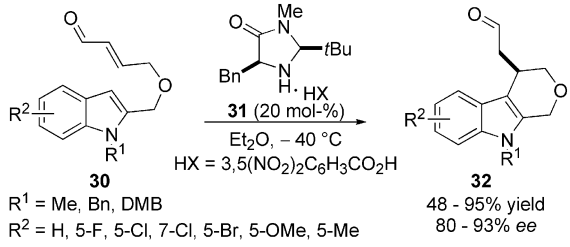
Scheme 7.

The syntheses of the alkaloids (–)-rhazinal, (–)-rhazinilam, (–)-leuconolam and (+)-*epi*-leuconolam were realized by the group of Banwell in where intramolecular F-C reactions authorized key transformations via carbon–carbon bond formation giving rise to the creation of complex structures (Scheme 8).[18,19]

In 2007, Xiao's group has also reported the intramolecular enantioselective organocatalyzed F-C alkylation of indoles via MacMillan's second generation imidazolidinone catalysts (Scheme 9).[20] In the presence of **31** (20 mol-%), a regio- and stereoselective (up to 93% *ee*) addition of a wide array of indole rings (e.g. electronic contributions and steric substituents did not disturb the reaction outcome) to the tethered α,β-unsaturated aldehydes **30** takes place in good yields (48–95%) to give tetrahydropyrano[3,4-*b*]indoles **32**.

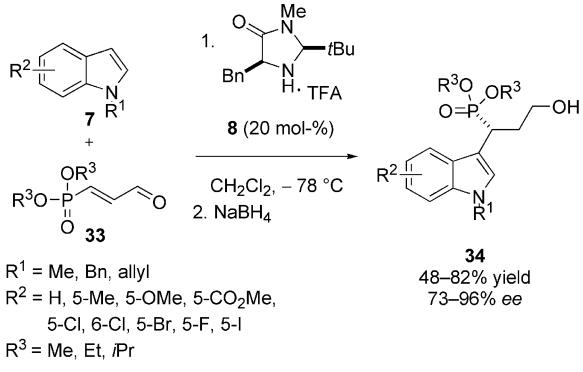


Scheme 8.



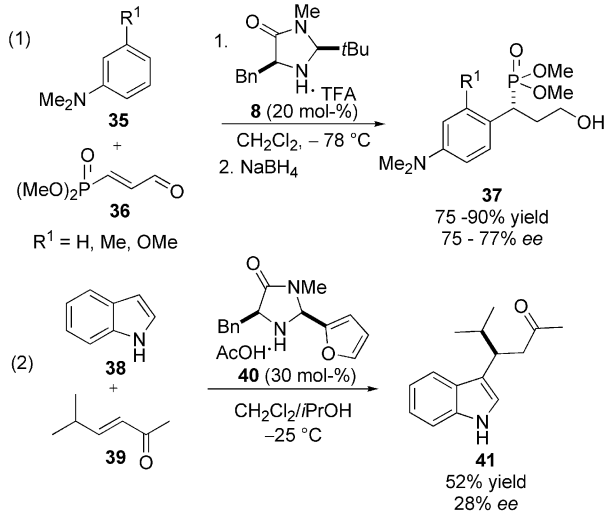
Scheme 9.

Two years later, the same group has developed an imidazolidinone-catalyzed addition of (*E*)-dialkyl 3-oxoprop-1-enylphosphonates **33** to indoles, that afforded α-indolyl phosphonates **34** (Scheme 10).[21] The reaction tolerates a variety of substrates with respect to both indole and dialkyl phosphorus scaffolds. With 20 mol-% of catalyst **8** at –78 °C in dichloromethane as solvent the alkylation was carried out in 48–82% yield and enantioselectivies ranged between 73 and 96% *ee*.



Scheme 10.

In the same publication,[21] they have extended the above mentioned methodology to aniline derivatives **35** and (*E*)-dimethyl 3-oxoprop-1-enylphosphonate (**36**). In this case, (*S*)-dimethyl 1-[4-(dimethylamino)phenyl]-3-hydroxypropylphosphonates **37** were prepared in 75–90% yields with 75–77% *ee* [Scheme 11, Equation (1)]. In addition, in 2006, they accomplished the first example of a F-C alkylation of indole (**38**) with 5-methyl-3-hexen-2-one (**39**) in a promising 52% isolated yield albeit in 28% *ee* [Scheme 11, Equation (2)].[22] In 2008, outstanding work on combining iminium and enamine catalysis in an asymmetric cascade transformation was published by Fréchet et al.[23] They devised a strategy in which incompatible catalyst systems were combined in one pot for sophisticated asymmetric multistep reactions via site isolation with star-soluble polymers.

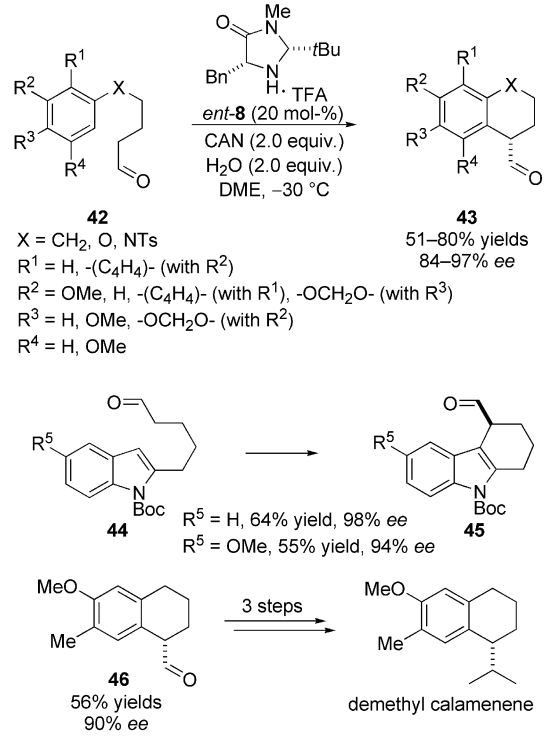


Scheme 11.

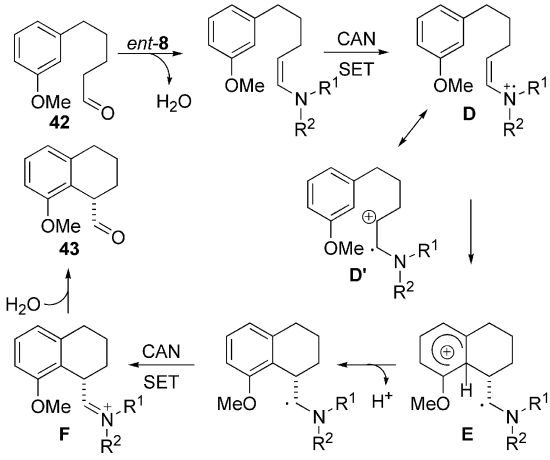
Recently, Nicolaou et al. have extended the concept of organo-SOMO catalysis, initially applied to α-functionalization of aldehydes,[24–27] to the intramolecular F-C type α-arylation of aldehydes incorporating electron-rich aromatic nuclei (Scheme 12).[28] In this transformation, a variety of bicyclic aldehydes **43** was isolated in good yields (51–80%) and enantioselectivities (up to 98% *ee*). The α-arylation takes place at –30 °C with 20 mol-% of catalyst *ent*-**8** in dimethyl ether (DME) as solvent with 2.0 equiv. of H_2O. As oxidant, cerium(IV) ammonium nitrate (CAN) was employed since other oxidants led to the decomposition of both substrate and catalyst. In the absence of H_2O as additive the same high enantioselectivy was observed albeit in a lower yield. The authors have elegantly homologated their methodology to the total synthesis of demethyl calamenene a cytotoxic product against human adenocarcinome A 549.

The authors suggest that the transformation takes place via enamine activation of aldehydes **42** with imidazolidinone *ent*-**8** (Scheme 13).[28b] Thus CAN-mediated single electron transfer (SET) oxidation gives rise to intermediate **D** (which is in equilibrium with **D′**) that quickly evolves to the more stable F-C intermediate **E**. Elimination of a hydrogen atom followed by a second SET oxidation affords **F** that over hydrolysis, gives rise to the observed bicyclic aldehydes **43**.

Independently, in the same year, MacMillan et al. published a similar enantioselective aldehyde α-arylation protocol using 1,3-disubstituted aryl rings.[29] Contrary to Nicolaou et al. who observed *para*-selectivity with electron-rich



Scheme 12.

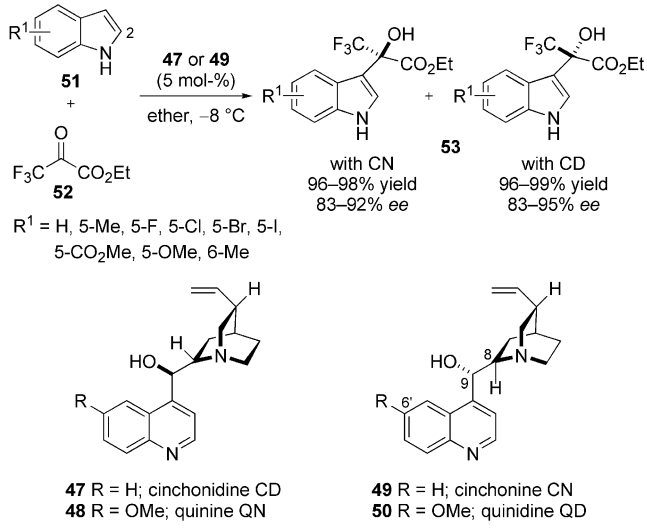


Scheme 13.

1,3,4-trisubstituted aryl rings,[28a] MacMillan's system showed to be highly *ortho*-selective. Based on their previous mechanistic studies into SOMO-activation, the authors assumed that for their substrates a radical based (open-shell) arylation pathway is effective. The methodology was used to devise a concise and enantioselective synthesis of (–)-tashiromine.

3. Cinchona Alkaloids

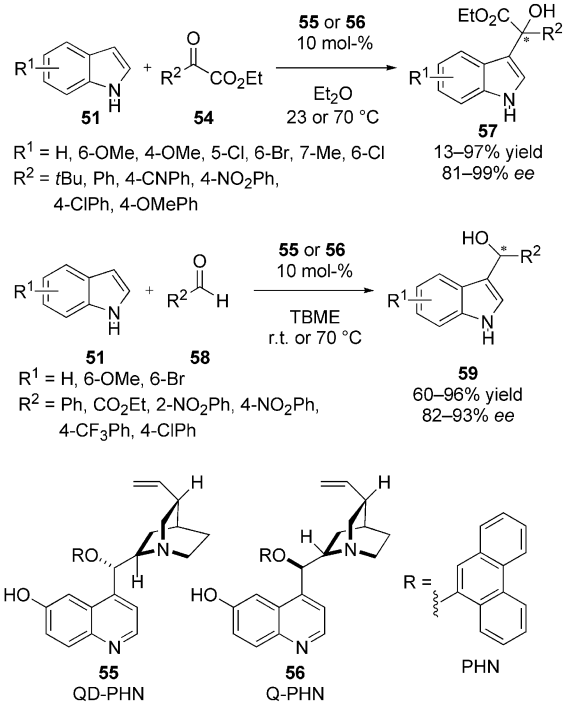
In 2005, cinchona alkaloids and derivatives[30] which are broadly used as effective organocatalysts in many asymmetric transformations were introduced as catalysts to accomplish F-C type reactions. Török, Prakash et al. have used such compounds in order to realize the enantioselective hydroxyalkylation of indoles with ethyl trifluoropyruvate (Scheme 14).[31] Only 5 mol-% of the cinchona alkaloid catalyst **47** or **49** at –8 °C was necessary for guiding the transformation with yields higher than 96% and up to 95% *ee*. During the screening of the reaction conditions, they have observed that the reaction outcome depended on the structural architecture of the catalyst. The best results were obtained with cinchonidine (**47**), cinchonine (**49**), quinine (**48**) and quinidine (**50**) in which both the nitrogen atom of the quinuclidine ring and the 9-hydroxy group are unprotected. By a judicious choice of the cinchona alkaloid catalyst both enantiomers of **53** can be easily synthesized. In order to reach the better compromise between yield and selectivity, indole NH framework cannot be blocked. Indeed, when the nitrogen of indole is protected by a methyl group only racemic mixture of products were isolated, regardless of good yields. The substituent at C-2 indole position also plays a crucial role for the enantioselection. With a sterically demanding substituent in the above mentioned position no enantiodifferentiation was observed and when a methyl group is present, the *ee* value of the product decreases (e.g. 95→75% *ee* with **47**; 90→64% *ee* with **49**). If mechanistic elucidation for this transformation is not yet fully understood, Török and Prakash suggested a H-bonded intermediate between the indole heterocycle **51**, the cinchona alkaloid and ethyl 3,3,3-trifluoropyruvate (**52**) in which the catalyst is not only responsible for the chiral environment but also for the activation of the carbonyl moiety of **52**.



Scheme 14.

The scope of the F-C hydroxyalkylation of indoles has been further extended with the communication by Deng et al. in 2006.[32] In this work, a broad variety of carbonyl compounds were used and the desired compounds were isolated in very good yields (52–97%) and enantioselectivities (83–99% *ee*) (Scheme 15). The reaction seems very general with either the indole ring **51** and the α-keto esters **54** (e.g. aryl, alkynyl or alkyl α-keto esters). Even at elevated tem-

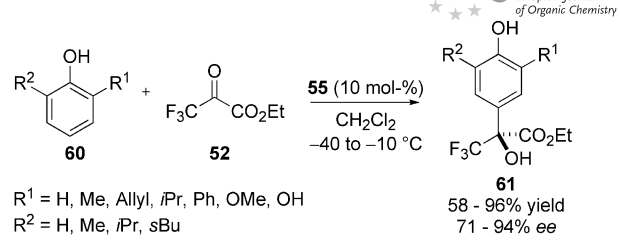
perature the enantioselectivity of the reaction remained high. When glyoxalate derivatives **58** were used instead of α-keto esters **54**, the reaction rate was faster and good yields (60–96%) and selectivities (82–93% *ee*) were reached. Better results were obtained when 10 mol-% of 6′-OH bifunctional cinchona alkaloids **55** (QD-PHN) or **56** (Q-PHN) were used to catalyze the hydroxyalkylation.



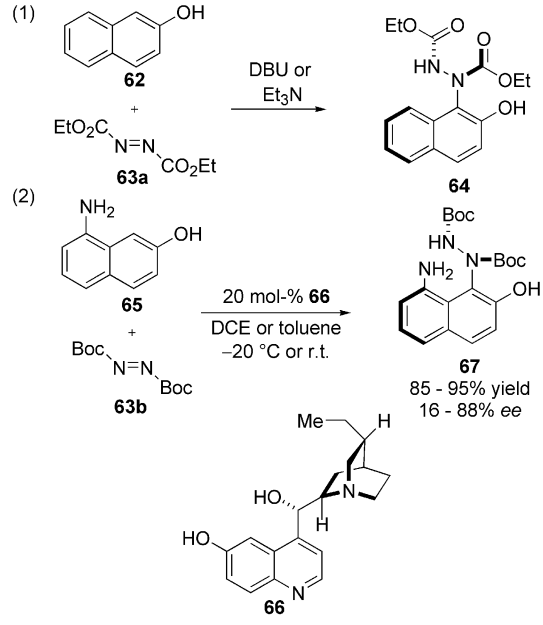
Scheme 15.

The first example of cinchona alkaloid mediated F-C alkylation of phenols with ethyl trifluoropyruvate was reported by Liu, Chen et al. in 2008 (Scheme 16).[33] It is known that simple phenol rings are less prompt to F-C alkylations since they are less carbon-nucleophiles than indoles or pyrroles. In addition, interactions between the free hydroxy group with the catalyst and complex transition state intermediates can conduct to low selectivities. They were delighted in observing that by using cinchona alkaloid derivatives a versatile and simple way to functionalize phenol rings was devised. The transformation takes place with a broad range of simple phenols **60** with excellent *para* regioselectivity. Among the cinchona alkaloids tested, the best compromise between yield and selectivity was encountered when derivative **55** was used instead of cinchonidine (**47**), quinine (**48**) or quinidine (**50**). The desired CF_3-containing α-hydroxy-α-aryl-carboxylate compounds **61** were isolated in good yields (58–96%) and enantioselectivities (71–94% *ee*).

Undoubtedly, an elegant application of cinchona alkaloids in the field of F-C transformations was reported in 2006 by Jørgensen's group.[34,35] In their work, the synthesis of a new class of non-biaryl atropisomers in which the nitrogen atom is directly bonded to the aromatic ring (e.g. carbamates or *N*,*N*-disubstituted 1-naphthamides) was accomplished via a F-C amination of 8-amino-2-naphthol derivatives. In a preliminary reaction trial, their results were quite intriguing since the reaction of simple 2-naphthol (**62**) and ethyl azodicarboxylate (**63a**) in the presence of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) or Et_3N conducted to a mixture of products in which the methylene groups of the carbamate scaffold are diastereotopics [Scheme 17, Equation (1)]. After HPLC analysis, they observed that the reaction gives rise to two enantiomers that can only be explained by a rotation on the N–C_{aryl} bond, thus creating atropisomers. Thus, in a first attempt to realize such a transformation in an enantioselective fashion, compound **65** and azodicarboxylate **63b** (that conducts to more stable atropisomers) were treated with 20 mol-% of dihydrocupreidine **66** and the required product **67** was isolated in good yields (85–95%) and up to 88% *ee* [Scheme 17, Equation (2)].[34]

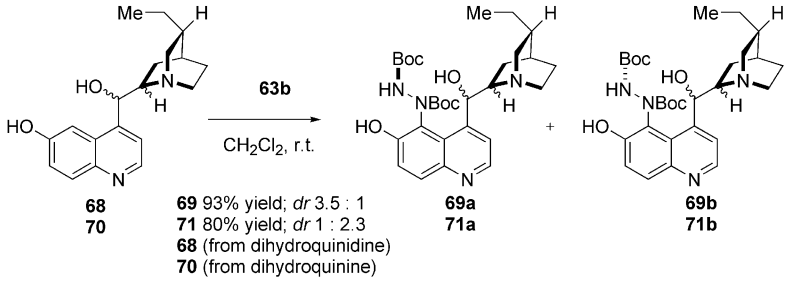


Scheme 16.



Scheme 17.

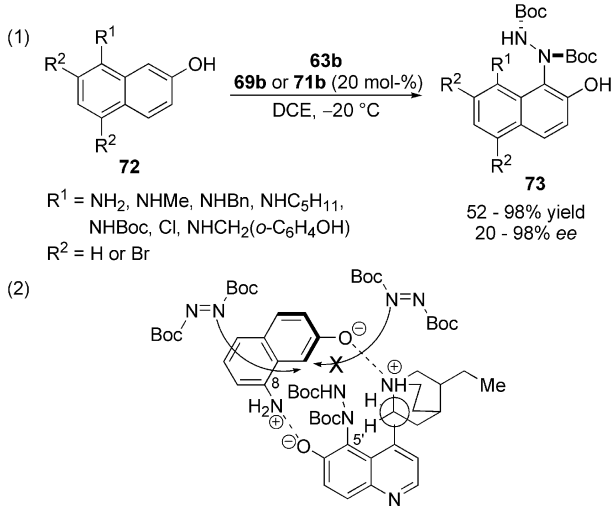
At this point of their studies, they experienced that the catalyst itself can also act as a substrate for the F-C reaction and, consequently, be aminated. In fact, in absence of 2-naphthol derivatives, dihydrocupreidines **68** and **70** were aminated in the presence of **63b** in CH_2Cl_2 as solvent at ambient temperature to give rise to two diastereoisomers (Scheme 18).



Scheme 18.

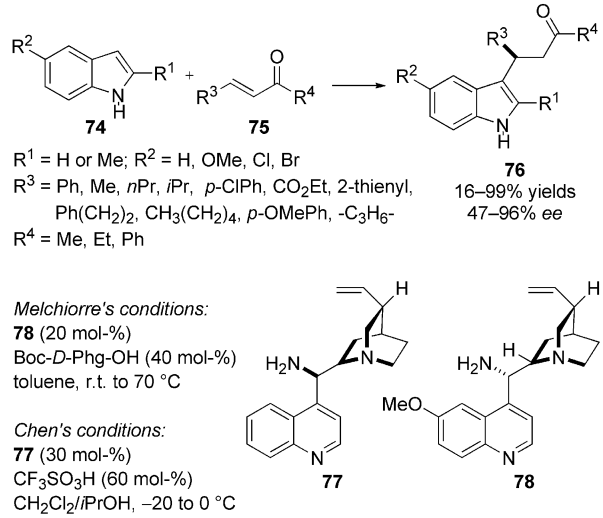
By using this methodology they were able to synthesize novel cinchona alkaloid derivatives that in turn can be expected to act as privileged catalysts in asymmetric transformations. As an example, the catalytic efficiency of the new synthesized compounds **69b** and **71b** was tested in the amination of 8-amino-2-naphthol derivatives. A significant improvement in the enantioselection of the transformation was observed compared with dihydrocupreidine **66** [Scheme 17, Equation (2)]. Based on their mechanistic observations, this enhanced enantioselectivity could be explained by the presence of the 5′-substituent (aminated hydrocupreidine) that shields one face of **72** directing the approach of **63b** to the less sterically hindered face. Another observation that was pointed out by the authors is the fact that ion pairing formation between the catalyst and the 2-naphthol derivative might also explain the high level of enantioselectivities that are only observed when the position C-8 is aminated [Scheme 19, Equation (2)].[35] The reaction seems quite general with respect to a variety of 8-amino-2-naphthols **72** and the desired products were isolated in good yields (52–98%) and moderate to excellent enantioselectivities (20–98% *ee*) [Scheme 19, Equation (1)]. It is noteworthy to mention, that the new cinchona alkaloids are bench stable solids and no epimerisation was observed even after months at room temperature for both diastereoisomers. In addition, the high functionality present in the final products **73** offers several possibilities for further elaborations that broaden the applicability of such interesting compounds.

In 2007, Chen's and Melchiorre's groups independently reported the enantioselective indole alkylation of α,β-unsaturated ketones via a chiral primary amine catalyst derived from natural cinchona alkaloids (Scheme 20).[36,37] Although this kind of reaction in the presence of α,β-unsaturated aldehydes has been well studied, the asymmetric F-C type alkylation of indoles with α,β-unsaturated ketones corresponds to a real challenge in organocatalyzed transformations. Both Chen's and Melchiorre's groups have anticipated that the formation of the iminium cation between the α,β-unsaturated ketone and a primary amine might be less hindered than with a secondary amine thus, much more suitable for enone activation. The results obtained by Chen's group showed that primary amine derivatives from cinchonine are effective and powerful catalysts for this less developed transformation.[36] The reaction tolerates a broad range of α,β-unsaturated alkyl ketones and in the presence



Scheme 19.

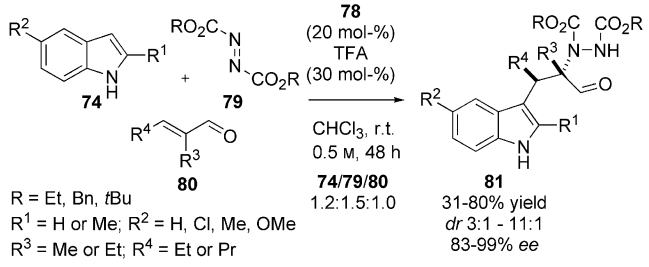
of 30 mol-% of catalyst **77** and 60 mol-% of acid co-catalyst CF_3SO_3H in CH_2Cl_2/*i*PrOH as solvent at –20 to 0 °C, moderate to excellent yields (16–99%) and good enantioselectivities (47–89% *ee*) were achieved for the transformation.



Scheme 20.

In the Melchiorre's work, the reaction also takes place in the presence of a counterion-directed organocatalytic system in which both catalyst (20 mol-%) and acid co-catalyst (40 mol-%) are chiral.[37] They have screened a series of *N*-protected L-amino acids as additives and intriguing results were obtained. First, the variation of the chiral structure of this latter seems to not affect the stereo-outcome of the reaction although the reactivity slightly decreases. Secondly, the absence of protection on the amine framework stops the catalytic cycle and no conversion was observed. Interestingly, using the racemic or the opposite enantiomer of the counterion gives rise to the same enantiomeric product with similar selectivity and reactivity levels. The best results being obtained with D-*N*-Boc-phenylglycine, this latter has been chosen as chiral additive by the authors to further investigate the scope of the reaction. In this case, the alkylation also seems general with respect to both indole and ketone architectures and the desired products were isolated in good yields (56–99%) and enantioselectivities (70–96% *ee*). They noticed that if the indolic nitrogen atom is protected by a methyl group low yield (<5%) and moderate enantioselectivity (62% *ee*) are achieved.

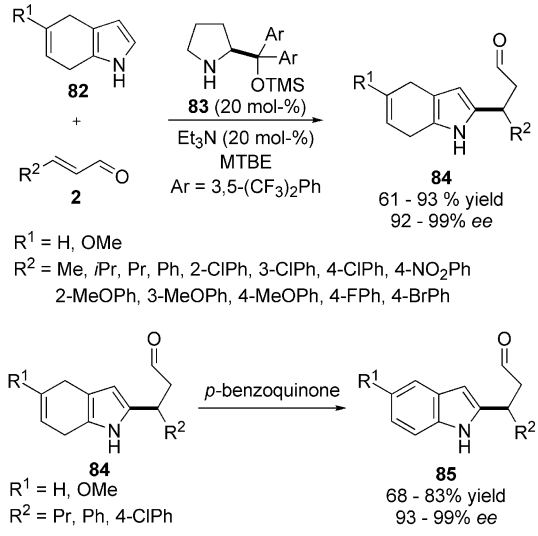
Very recently, Melchiorre et al. have also devised an elegant example of F-C reaction in which an organocascade strategy was employed (Scheme 21).[38] The transformation takes place by mixing catalyst **78** (20 mol-%) at room temperature in chloroform with indole rings, α,β-unsaturated aldehydes and azodicarboxylates. A great deal of reaction optimization was necessary in order to find convenient reaction conditions since such combination of starting materials could afford a complex mixture of products as the result of cross-reactions. However, the desired compounds **81** were isolated in moderate to good yields (31–80%) and good selectivities (*dr* 3:1→11:1; 83–99% *ee*).



Scheme 21.

4. Diarylprolinol Ethers

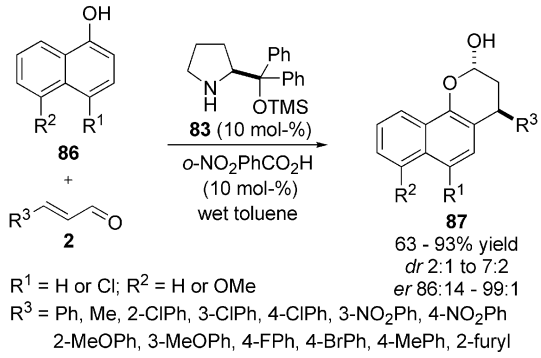
Since the discovery of diarylprolinol derivatives as organocatalysts in 2005 by Jørgensen's[39] and Hayashi's[40] groups, this class of compounds has still proven its ability for catalyzing a plethora of very important transformations in the field of asymmetric synthesis allowing to highly functionalized entities with very interesting chemical properties.[41] Although this class of organocatalysts has been well used for activating simple or α,β-unsaturated aldehydes for α- and/or β-functionalization, γ-functionalization and cascade reactions, until 2009 no example of F-C alkylation has been reported. Wang et al. were the first to devise three efficient methodologies in which such catalysts were used for guiding F-C alkylations. Through the use of 20 mol-% of **83** and 20 mol-% of Et_3N as additive in *tert*-butyl methyl ether (MTBE) as solvent at ambient temperature, enantioselective F-C alkylation of 4,7-dihydroindoles **82** with α,β-unsaturated aldehydes **2** has been realized in good yields (61–93%) and excellent enantioselectivities (92–99% *ee*) (Scheme 22).[42] The reaction tolerates important variations concerning the unsaturated aldehyde structures and electronic environment. By oxidation of the 2-substituted 4,7-dihydroindoles **84** with *p*-benzoquinone the less common 2-substituted indole derivatives **85** could be isolated in high yields without any erosion of the enantioselectivity. Hence, this procedure complements existing previously described herein methods in which F-C alkylations of indoles allow to the 3-substituted indole entities.



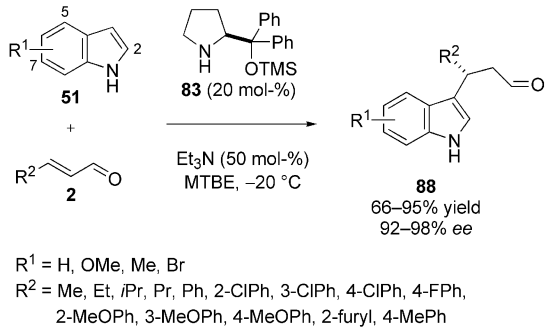
Scheme 22.

The enantioselective synthesis of chromanes and dihydrobenzopyranes has been devised by Wang et al. via a Michael-type F-C alkylation of 1-naphthols and α,β-unsaturated aldehydes followed by a cyclization reaction (Scheme 23).[43] The cascade transformation takes place in the presence of 10 mol-% of catalyst **83** and 2-nitrobenzoic acid as additive in wet toluene as solvent (yields ranging from 63 to 93%; *dr* up to 7:2 and up to 99:1 *er*). The stereo-outcome of the reaction seems to be directly related to the electronic environment of the α,β-unsaturated aldehydes, although a broad scope of this latter could be tolerated. Better yields and enantioselectivities were obtained when electron-withdrawing groups were present in the aldehyde structures. No conversion was detected when simple phenol has been used.

Very recently, they have shown that a dual Lewis-base/Lewis-base bifunctional catalysis can give rise to 3-substituted indoles, thus providing a supplementary method for such transformation (Scheme 24).[44] The idea was to employ diphenylprolinol silyl ethers for the activation of α,β-



Scheme 23.



Scheme 24.

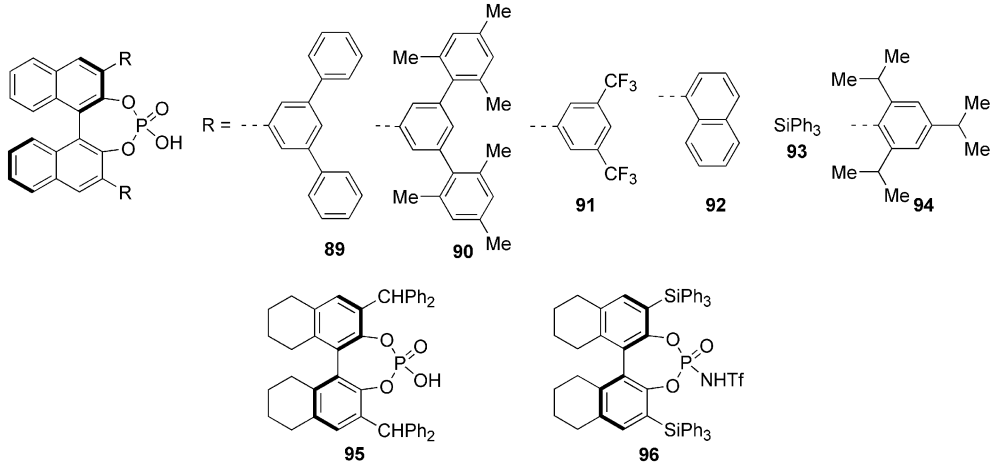
unsaturated aldehydes and triethylamine for the deprotonation or H-bonding activation of the indole ring. The optimal conditions rely on the use of 20 mol-% of catalyst **83**, 50 mol-% of triethylamine in *tert*-butyl methyl ether (MTBE) as solvent at –20 °C. As shown in Scheme 24, various α,β-unsaturated aldehydes **2** and indoles containing electron-withdrawing or electron-donating C-5 substituents **51** can be tolerated. Good levels of enantioselectivities are reached when the C-2 or the C-7 indole positions are alkylated, albeit with slight lower reactivity. Substitution on the indolic nitrogen atom has a detrimental effect on both selectivity and reactivity, which is believed to be related to the impossibility of *N*-substituted indole being deprotonated by the triethylamine.

Independently, in the same year, analogous work on the F-C alkylation of indoles with aromatic α,β-unsaturated aldehydes via **83** (20 mol-%) has been published by Bao et al.[45] In their work there is no need for further additive and the products are isolated in good yields (56–87%) and high enantioselectivities (86–98% *ee*).

In 2009, organocatalytic conjugate addition followed by acid-mediated electrophilic aromatic substitution were elegantly employed by Franzén and Fisher to prepare indolo[2,3*a*]quinolizidine and benzo[2,3*a*]quinolizidine derivatives.[46] Although moderate diastereoselectivities were reached, the one-pot transformation allows the creation of three new stereocenters in excellent enantioselectivities.

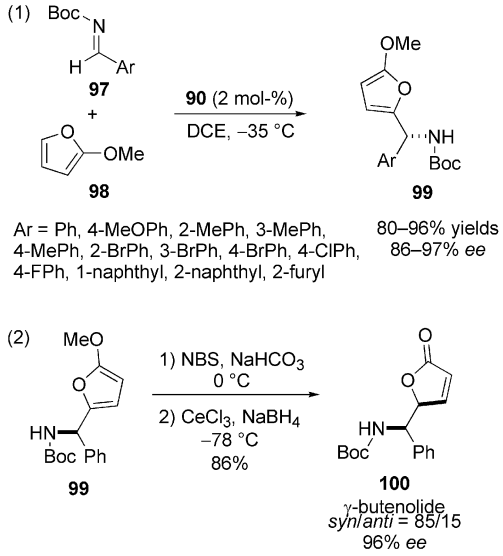
5. Phosphoric Acids

If the activation of an electrophile by means of a Brønsted acid is one of the most classical ways to promote a reaction, development of this type of catalysts in an asymmetric form was limited. Indeed, the conception of Brønsted acid catalysts able to create a chiral environment and consequently to induce stereoselectivities for a reaction was until very recently unachieved. However, in 2004, the pioneering works of Akiyama[47] and Terada[48] on enantioselective Mannich-type reactions proved that chiral phosphoric acids derived from binaphthol could efficiently catalyze asymmetric transformations by activation of imine derivatives.[49,50] These results opened the way to the use of this new type of organocatalysts in asymmetric F-C reactions. Scheme 25 lists all the phosphoric acids used in this part, they are all based on a binaphthol or octahydrobinaphthol structure bearing bulky substituents at the C-3 and C-3′ positions.



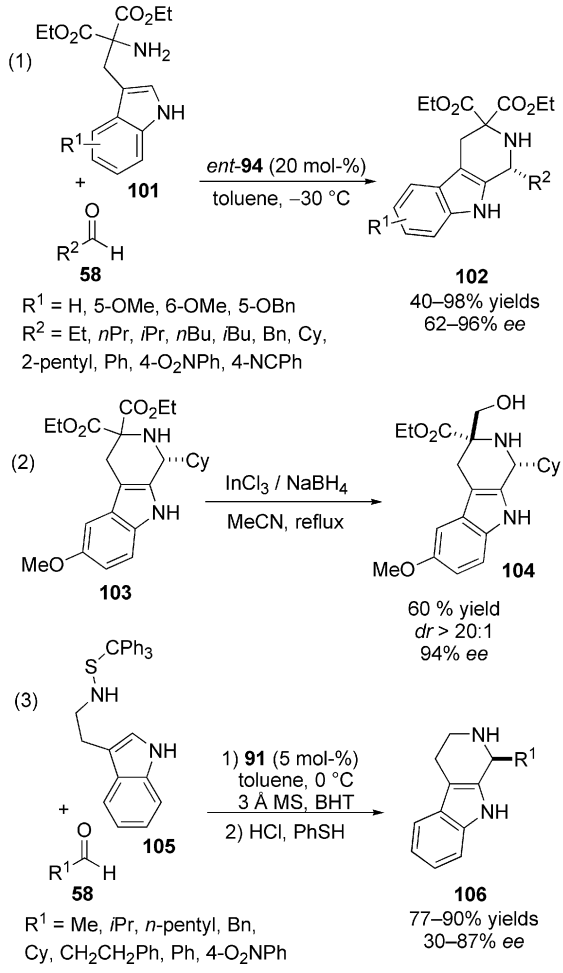
Scheme 25.

The first example of an asymmetric F-C reaction organocatalyzed by phosphoric acids was reported in 2004 by Terada et al. [Scheme 26, Equation (1)].[51] The alkylation of 2-methoxyfuran **98** with *N*-Boc aldimines **97** can be efficiently carried out at low temperature (–35 °C) using 2 mol-% of very bulky catalyst **90** and the expected furan-2-ylamines **99** are isolated in good yields (80–96%) and stereoselectivities (up to 97% *ee*). A wide range of aromatic aldimines **97** is tolerated in the reaction: substitution of the phenyl ring at the *ortho*, *meta* and *para* position, as well as naphthyl and furyl substrates have been tested and all give similar results. Noteworthy, this F-C alkylation also proceeds smoothly in a gram scale with a catalyst loading as low as 0.5 mol-% without any deleterious effect on the yield and the selectivity. Moreover, to prove the synthetic utility of their reaction, the authors described the derivatization of the furan ring (**99**, Ar = Ph) to γ-butenolide (**100**) in two steps without any loss of optical purity [Scheme 26, Equation (2)].



Scheme 26.

In 2006, List et al. described the use of chiral phosphoric acids in a catalytic asymmetric Pictet-Spengler[52] reaction [Scheme 27, Equation (1)].[53] The reaction between geminally disubstituted tryptamines **101** with aldehydes **58** occurs at low temperature (–30 °C) in the presence of 20 mol-% of catalyst loading (*ent*-**94**) allowing the access to tetrahydro-β-carbolines **102** in good to excellent yields (40–98%) and stereoselectivities (up to 96% *ee*). Various aliphatic aldehydes (**58**) as well as aromatic substrates bearing electron-withdrawing groups can be efficiently employed in this reaction. The disubstitution of the tryptamine derivatives **101** by ester functions is crucial to limit the formation of side products from aldol condensations and represents a limitation in the methodology. However, List's group have demonstrated that the diester **103** can be used for further interesting transformations such as a highly diastereoselective reduction (*dr* > 20:1) of only one ester function providing the mono-alcohol **104** with one additional chiral center in 60% yield [Scheme 27, Equation (2)].

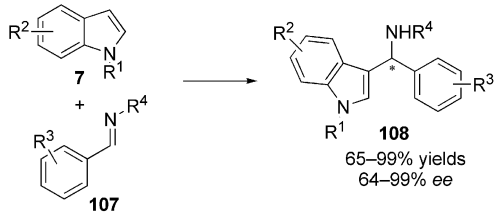


Scheme 27.

More recently, Hiemstra et al. reported an improvement in the asymmetric Pictet-Spengler reaction by using sulfenyl-substituted tryptamines **105** (readily prepared from treatment of the amine with a commercially available sulfenyl chloride) as substrates [Scheme 27, Equation (3)].[54] Indeed, the sulfenyl group stabilizes the intermediate iminium ion and facilitates the intramolecular cyclization over undesired intermolecular aldol condensations. In this case, the geminal disubstitution of the tryptamine becomes unnecessary, which widens the scope of the organocatalyzed Pictet-Spengler reaction. The sulfenyl group can be easily cleaved, after the cyclization step, by treatment in acidic conditions followed by neutralization to give the tetrahydro-β-carbolines **106** in good yields (77–90%) and selectivities (up to 87% *ee*).

Afterwards, the use of indole substrates in intermolecular F-C reactions catalyzed by phosphoric acids was independently described by three groups in 2007. You et al. developed the addition of indoles **7** to *N*-sulfonylaldimines **107** (Scheme 28).[55] The expected 3-indolylmethanamines **108** are synthesized in good yields (68–94%) and excellent

enantioselectivities (up to 99% *ee*) when the reaction is performed at low temperature (–60 °C) with 10 mol-% of catalyst loading (*ent*-**92**). Substitution of the indole ring either with electron-withdrawing or electron-donating groups is well-tolerated in these conditions. Moreover, a wide range of aldimines **107** have been tested. For this latter, the best results are obtained with electron-donating substituents on the phenyl ring whereas a slight drop in the enantioselectivity is observed by introducing electron-withdrawing substituents. In the case of an aliphatic imine (derived from cyclohexylaldehyde), the corresponding 3-indolylmethanamine **108** is prepared in only a moderate yield (56%) and selectivity (58% *ee*). Very recently, the same group showed that these indolylmethanamines could be used as electrophilic susbtrates for a subsequent F-C reaction with another electron-rich arene allowing the access to interesting unsymmetrical triarylmethanes.[56]



R^2 = H, 5-OMe, 5-Me, 5-Br, 5-CO_2Me, 6-Cl, 7-Me, 2-Me
R^3 = H, 4-Me, 4-*i*Pr, 4-Ph, 4-OMe, 4-F, 4-Cl, 4-Br, 4-CF_3, 4-NO_2, 3-Me, 3-OMe, 3-F, 3-Cl, 3-NO_2, 2-Me, 2-OMe, 2-F

You's conditions:
ent-**92** (10 mol-%), toluene, –60 °C
R^1 = H, R^4 = Ts, Bs

Terada's conditions:
89 (2-10 mol-%), $(CHCl_2)_2$, –40 °C
R^1 = TBS, R^4 = Boc

Antilla's conditions:
ent-**93** (5 mol-%), 4Å MS, CH_2Cl_2, –30 °C
R^1 = Bn, R^4 = Bz

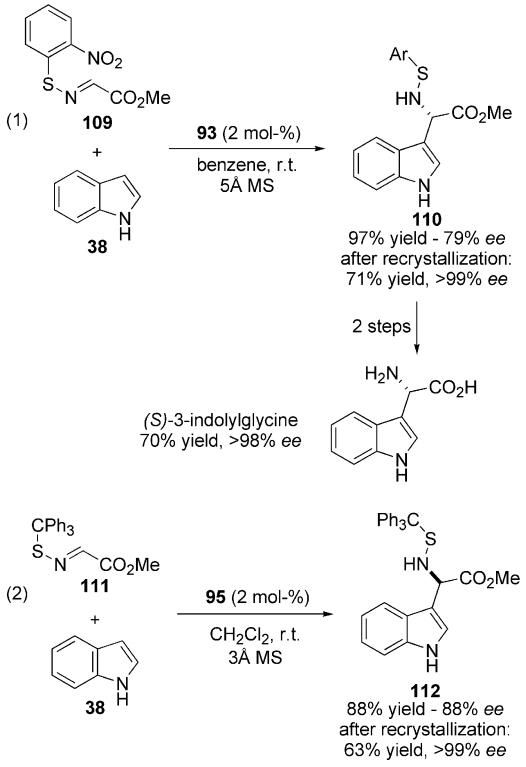
Scheme 28.

Terada et al. reported the reaction of *N*-TBS indoles **7** with *N*-Boc aldimines **107** (Scheme 28).[57] The F-C alkylation at the C-3 position of the indole rings occurs at low temperature (–40 °C) and with low catalyst loadings (2 mol-% of **89** in most cases) providing the expected indolylmethanamines **108** with good yields (65–91%) and remarkable selectivities (83–98% *ee*). The influence of the substitution of both the indole **7** and the aromatic aldimine **107** on the outcome of the reaction has been investigated. Similar results are obtained regardless of the electronic nature of the substituents. In the particular case of *ortho* substituents on the aldimines, the reaction appears to proceed much slowly and higher catalyst loadings (10 mol-%) are required to isolate the desired products in acceptable yields.

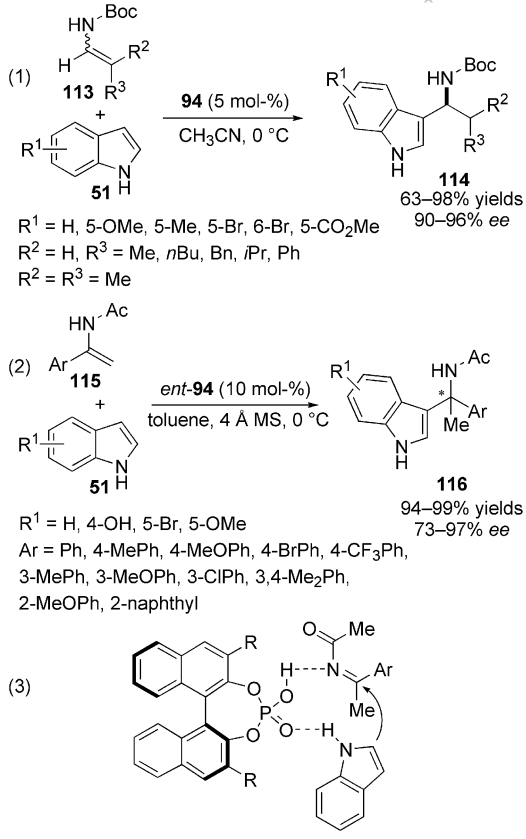
Antilla et al. also described a F-C alkylation of *N*-alkyl indoles **7** starting from *N*-benzoylaldimines **107** (Scheme 28).[58] The expected indolylmethanamines **108** are obtained in very good yields (89–99%) and enantioselectivities (up to 97% *ee*) proceeding at low temperature (–30 °C) with 5 mol-% loading of catalyst *ent*-**93** based on a binaphthyl structure substituted with two bulky triphenylsilyl groups. The benzyl protection of the nitrogen atom on the indole moiety is required to ensure a good stereoselectivity in the reaction. Indeed, when the procedure is applied to unprotected or *N*-methyl indole, only poor enantiomeric excesses are observed (30% *ee*). Substitutions on both the indole **7** and the aldimine **107** are well-tolerated. The reaction gives similar results, even with *ortho* substituted aldimines. The more sterically hindered 2-methylindole appears to be the only substrate which provides lower selectivity (64% *ee*).

The F-C reaction between aldimines and indoles was further developed by Enders et al. for the asymmetric synthesis of isoindolines,[59] and by Ma et al. using in situ generated imines derived from trifluoroacetaldehyde.[60] In 2008, Hiemstra et al. applied the asymmetric F-C alkylation of indoles catalyzed by chiral phosphoric acids to the preparation of enantiopure 3-indolylglycine, a nonproteogenic α-amino acid (Scheme 29).[61] Their synthesis employs *N*-sulfenyl protected imines derived from methyl glyoxylate (**109** and **111**) as the starting materials. Interestingly, the nature of the sulfenyl group has an important influence on the reaction outcome. The two tested sulfenyl protecting groups require different optimized reaction conditions and provide the two different enantiomers of the target 3-indolylglycine (Scheme 29). In both cases, the protected amino acids (**110** and **112**) are obtained in good yields (97 and 88%) and respectable enantioselectivities (79 and 88% *ee*) which can be improved after recrystallization to give the enantiopure products (>99% *ee*). Moreover, the unprotected form of (*S*)-3-indolylglycine has been prepared in two additional steps with a good yield (70% over 2 steps) and without significant loss of selectivity [Scheme 29, Equation (1)]. More recently, a broad range of substituted 3-indolylglycines were prepared in good yields (85–93%) and selectivities (51–87% *ee*) using the same methodology by You et al.[62]

Not only aldimines were used in the F-C alkylation of indoles via phosphoric acids catalysis. In 2007, Terada et al. reported that electron rich alkenes, like *N*-Boc protected enamines **113**, could also serve as substrates in the reaction and conduct to the expected 1-indolyl-1-alkylamines **114**, a new series of asymmetric indolylmethanamines [Scheme 30, Equation (1)].[63] Good yields (63–98%) and selectivities (90–96% *ee*) are observed when the reaction is carried out at 0 °C with 5 mol-% of catalyst loading (**94**). Enamines **113** bearing a linear, a branched alkyl group or an aromatic substituent are all well-tolerated. Even a more sterically hindered disubstituted substrate [Scheme 30, Equation (1), $R^2 = R^3$ = Me] is suitable for the procedure. A broad array of indoles **51** has also been tested and gives uniform results. Noteworthy, both isomers (*E*) and (*Z*) of the enamines **113** can be employed, providing the same enantiomers of the desired indolylalkylamines **114** with the same level of selectivity. This observation suggests that the reaction proceeds



Scheme 29.



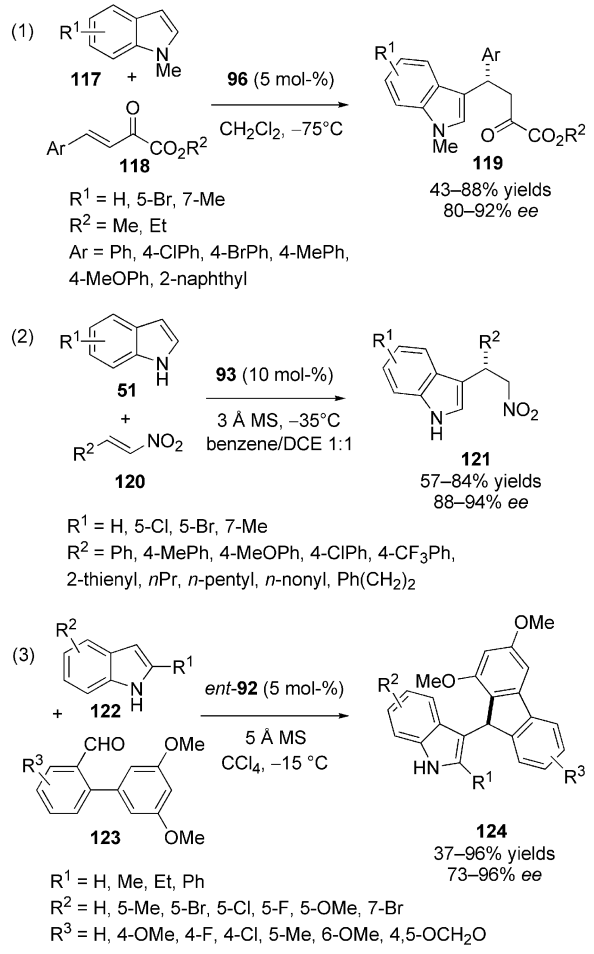
Scheme 30.

through the common imine intermediate generated by the tautomerization of the *N*-protected enamine **113** in the first step.

The same year, Zhou et al. described the use of the *N*-protected enamine substrates **115** to synthesize indolylethylamine **116** possessing a quaternary asymmetric center [Scheme 30, Equation (2)].[64] The reaction between the indole **51** and the α-aryl enamine derivative **115** proceeds smoothly in toluene at 0 °C with 10 mol-% of catalyst loading (*ent*-**94**), enabling the preparation of the desired chiral amines **116** with a quaternary carbon atom in excellent yields (94–99%) and good enantioselectivities (up to 97% *ee*). The scope of the methodology appears to be quite wide. The α-aryl enamines **115** with either an electron-withdrawing or donating substituent at the *meta* or *para* position of the phenyl ring give similar high selectivities. Only the *ortho* substitution seems to affect the course of the reaction decreasing both the reactivity and the selectivity. Interestingly, the presence of the nitrogen–hydrogen bond in both the enamine **115** and the indole **51** is crucial to the reaction since no conversion of the starting materials is observed using either *N*-methylindole or *N*-acetyl-*N*-methylenamine. Indeed, the *N*-methylated enamine cannot be converted into its ketimine form which seems to be the key intermediate in the reaction. The absence of reactivity of *N*-methylindole supports the existence of a hydrogen-bond between the indole **51** and the phosphoric acid catalyst *ent*-**94** that enhances the nucleophilicity of the heteroaromatic ring and directs the attack on the activated ketimine [Scheme 30, Equation (3)].

If chiral phosphoric acids are most commonly applied to the activation of imine derivatives, Rueping et al. used an acidic *N*-triflylphosphoramide **96** derived from this family of catalysts to promote the F-C alkylation of indoles **117** with β,γ-unsaturated α-keto esters **118** as electrophiles [Scheme 31, Equation (1)].[65] The expected Michael adducts **119** can be prepared in good yields (43–88%) and enantioselectivities (up to 92% *ee*) when the reaction is performed at low temperature with 5 mol-% catalyst loading (**96**). Noteworthy, several other Brønsted acids containing a binaphthol core were tested for this reaction and all conducted to the formation of the 1,2 adducts as the major products, which proves the superior steric properties of **96** that prevent direct addition on the carbonyl. The same family of electrophiles was recently employed by Zhou, He et al. and Acocella et al. who reported the F-C alkylation of indoles with α,β-unsaturated aromatic ketones in good yields (36–98%) but moderate selectivities (18–56% *ee*).[66] In 2009, You et al. also described the activation of α,β-unsaturated ketones by phosphoric acids in an intramolecular F-C alkylation of indoles.[67] Noteworthy, the unsaturated ketones suitable for this procedure were prepared by a cross-metathesis reaction performed sequentially in the same pot as the F-C cyclization with excellent results (43–97% yield, 80–94% *ee*).

In 2008, Akiyama et al. proved that nitroalkenes **120** could be efficiently activated by phosphoric acids to promote F-C reactions [Scheme 31, Equation (2)].[68] Indeed,

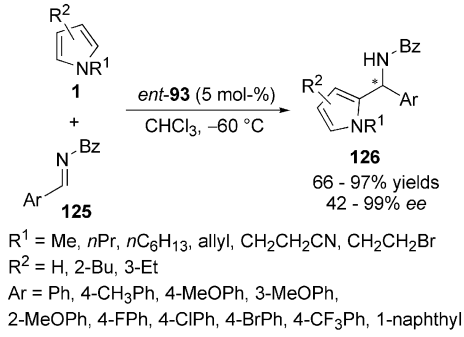


Scheme 31.

the desired 3-alkylated indoles **121** are isolated in good yields (57–84%) and selectivities (88–94% *ee*) working at low temperature (–35 °C) with 10 mol-% of chiral catalyst **93**. The addition of molecular sieves into the reaction mixture is crucial for both the reactivity and the selectivity. Various substituted indoles **51** or nitroalkenes **120** were employed in the procedure and all provided similar results, although aliphatic nitroalkenes appeared to be less reactive and required longer reaction time.

More recently, You et al. described the use of phosphoric acids for the catalysis of a tandem double F-C reaction [Scheme 31, Equation (3)].[69] Catalyst *ent*-**92** efficiently activates an aldehyde function to promote a classical intermolecular F-C alkylation of indole and facilitates the formation of a carbocation from the intermediate alcohol providing the corresponding 9-(3-indolyl)fluorenes **124** through an intramolecular F-C reaction in good yields (37–96%) and very interesting selectivities (up to 96% *ee*). The authors suggest that the control of the selectivity may be explained by the proximity between the carbocation and its phosphate counterion which creates a chiral environment. Substitution of both the indole **122** and the biphenyl **123** starting materials seems to be well-tolerated in the procedure. The presence of a substituent at the C-2 position of the indole ring is required to avoid the formation of byproducts and consequently to obtain high yields. As previously observed with cinchona alkaloids (Schemes 14, 15 or 16), the activation of carbonyl compounds for the 1,2-addition of aromatic nucleophiles was also reported by Ma et al. They prepared trifluoromethylated tertiary alcohols in excellent yields (52–99%) and selectivities (up to 99% *ee*) starting from trifluoromethyl ketones and variously substituted indoles.[70]

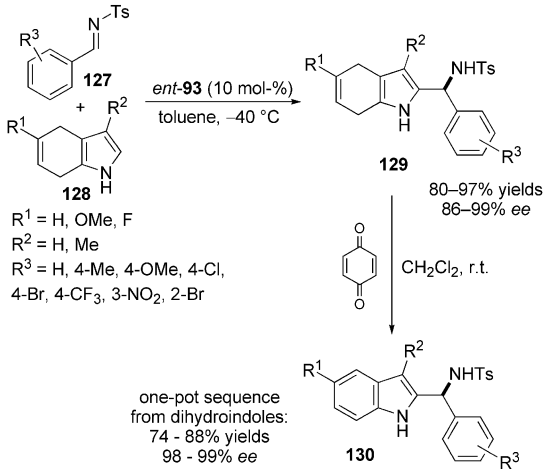
After the extensive studies on the F-C alkylation of indole heterocycles catalyzed by chiral phosphoric acids, Antilla et al. envisioned substituted pyrroles **1** as suitable substrates in this type of reaction (Scheme 32).[71] The F-C alkylation of pyrroles **1** with *N*-benzoyl imines **125** takes place at low temperature (–60 °C) and with 5 mol-% catalyst loading (*ent*-**93**) giving the expected 2-pyrroylmethanamines **126** in good to excellent yields (66–97%) and with moderate to excellent selectivities (42–99% *ee*). The reaction is rather sensitive to both the substitution on the pyrrole ring and the aryl imine **125**. Electron-donating substituents in the *para* or *meta* position enable to obtain the F-C adducts with excellent yields and selectivities whereas either electron-withdrawing groups or substituents in *ortho* give lower enantiomeric excesses. The nature of the nitrogen atom substituent on the pyrrole **1** has a great influence on the results. Indeed, the N-H pyrrole substrate gives the alkylated product with a poor enantiomeric excess (14% *ee*) and a decrease in the stereoselectivity is observed when the length of the *N*-alkyl substituent is increased, probably due to a more important steric hindrance. Moreover, the presence of a substituent at the C-2 or C-3 position of the pyrrole **1** has also a deleterious effect on the selectivity. In 2009, Nakamura et al. reported the use of unprotected pyrrole in the F-C alkylation with *N*-(2-*p*yridylsulfonyl)imines to obain the 2-pyrroylmethanamines in moderate to good yields (11–80%) and good selectivities (up to 95% *ee*).[72] Nitroolefins were also recently employed by You et al. to functionalize pyrrole heterocyles with good results (81–94% yield, up to 94% *ee*).[73]



Scheme 32.

4,7-Dihydroindoles were employed for the first time in 2008 by You et al. as nucleophilic substrates in organocatalyzed F-C reactions using different types of electrophiles.[74] With *N*-tosyl aldimines **127** (Scheme 33), the reaction proceeds in 5–80 min at low temperature (–40 °C) affording the expected 2-alkylated 4,7-dihydroindoles **129** in excellent

yields (80–97%) and selectivities (86–99% *ee*).[74a] Substitution on the dihydroindole **128** or the imine **127** does not seem to affect the results, only the presence of an *ortho* substituent on the imine produces a slight drop in both the reaction rate and the enantiomeric excess. The 4,7-dihydroindole **129** can be oxidized with *p*-benzoquinone providing access to the corresponding 2-alkylated indoles **130**, which cannot be prepared by the direct F-C alkylation on indoles. The sequence F-C/oxidation has been performed in a one-pot procedure allowing the isolation of the expected 2-indolylmethanamines **130** in good overall yields (74–88%) and excellent enantioselectivities (98–99% *ee*). The same strategy for the asymmetric synthesis of 2-substituted indoles was also applied to the use of β,γ-unsaturated α-keto esters[74b] and nitroolefins[74c] as electrophiles in the F-C reaction with similar good results. Noteworthy, in the latter case, slow addition of nitroolefin electrophiles via syringe pump enabled to lower the catalyst amount necessary to perform the reaction to 0.5 mol-%, a particularly interesting catalyst loading in organocatalysis.

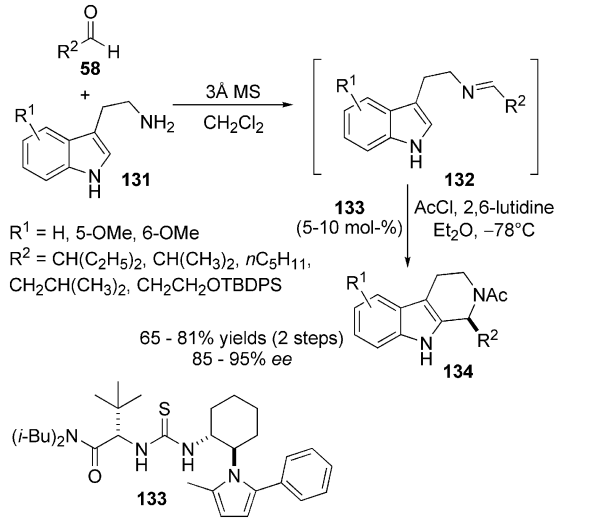


Scheme 33.

6. Thioureas

Since the first reports by Jacobsen et al. on asymmetric Strecker reaction catalyzed by a chiral thiourea,[75] this new type of organocatalyst has proved its efficiency to promote a wide range of asymmetric transformations.[50,76] Chiral thiourea derivatives, easily prepared by the addition of a primary amine on an isothiocyanate, are particularly good hydrogen-bond donors which can bind with a variety of electrophiles containing heteroatoms. Thus, they act by enhancing the reactivity of the latter and creating a chiral environment around them. Several examples of the use of this family of organocatalysts in the asymmetric F-C reaction have been described so far.

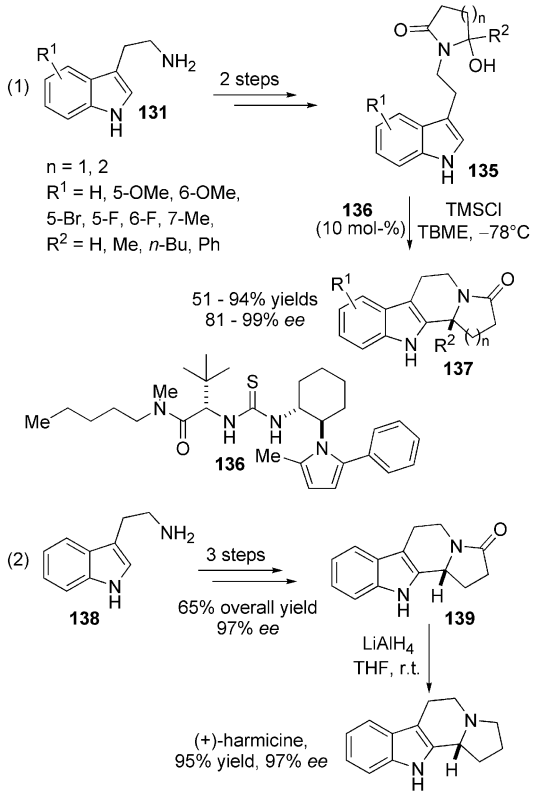
Pionneering work on chiral thiourea derivatives mediated asymmetric F-C reaction was reported in 2004 by Jacobsen et al. (Scheme 34).[77] The enantioselective Pictet-Spengler reaction producing chiral tetrahydro-β-carbolines **134** can be efficiently performed at low temperature (–78 °C) using a dual activation process. Indeed, the thiourea catalyst **133**, incorporating a chiral diaminocyclohexane moiety, fails to promote the intramolecular cyclization reaction of imines **132** derived from tryptamine **131**, when it is employed alone. The addition in the reaction medium of an acylating agent allows the formation of a more reactive *N*-acyliminium intermediate, which readily reacts under the supplementary activation of the catalyst **133**. The expected *N*-acyl tetrahydro-β-carbolines **134** are obtained in good yields (65–81%) and high selectivities (up to 95% *ee*) employing 5–10 mol-% catalyst loadings. Similar results are observed with different aliphatic aldehydes **58**, but the procedure cannot be successfully applied to aromatic or sterically hindered aldehydes (like trimethylacetaldehyde).



Scheme 34.

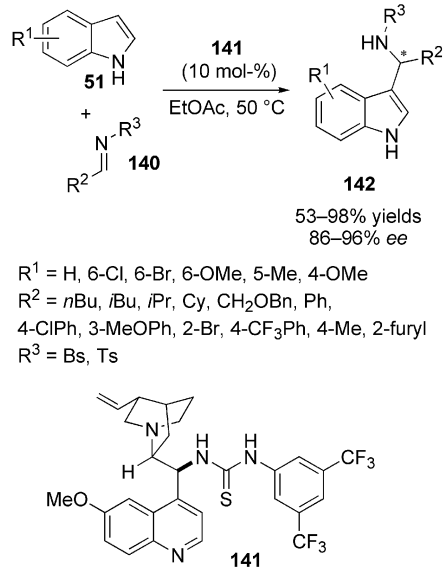
In 2007, the same group described a variation of their previous methodology.[78] They used hydroxylactams **135**, easily synthesized in two steps from tryptamine **131** and succinic or glutaric acid, in a Pictet-Spengler type reaction to obtain enantioenriched indolizidinones and quinolizidinones **137** [Scheme 35, Equation (1)]. The reaction is performed at low temperature (–78 °C) with 10 mol-% of catalyst **136** and chlorotrimethylsilane as activating agent. Good-to-excellent yields (51–94%) and selectivities (81–99% *ee*) are observed starting from a broad variety of succinimide or glutarimide precursors. The substitution of the indole ring with either electron-withdrawing or electron-donating groups is well-tolerated. This efficient procedure has been applied to the total synthesis of (+)-harmicine [Scheme 35, Equation (2)] which can be obtained in only four steps in good overall yield (62%) and excellent enantioselectivity (97% *ee*). Accordingly to the authors' proposed mechanism for this Pictet-Spengler-type cyclization, the reaction of the hydroxylactam with chlorotrimethylsilane is supposed to rapidly conduce by dehydration to the formation of a *N*-acyliminium, the electrophilic species in the F-C alkylation. The thiourea catalyst is assumed to promote the enantioselective cyclization by binding the

chloride counterion, thus creating a chiral *N*-acyliminium chloride-thiourea complex and inducing dissociation of the ion pair. This hypothesis seems to be confirmed by the important effect of the halide counterion on the reaction: replacing the chloride by a bromide or iodide does not affect the reactivity but decreases the enantiomeric excess (only 5% *ee* with an iodide).



Scheme 35.

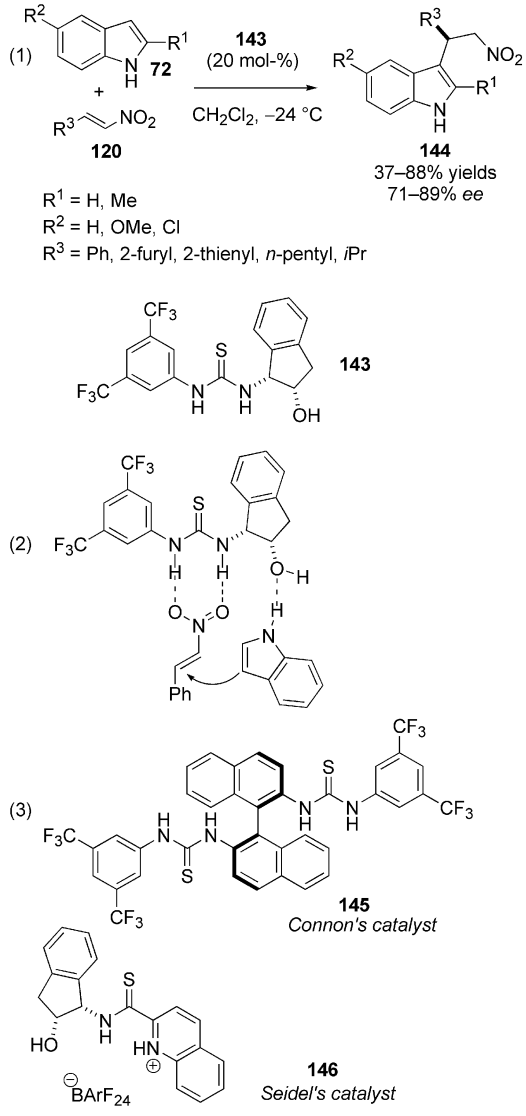
In 2006, Deng et al. developed the asymmetric synthesis of 3-indolyl methanamines **142** using as catalyst chiral thiourea **141**, functionalized with a cinchona alkaloid (Scheme 36).[79] The reaction performed at 50 °C allows to isolate the F-C products in good yields (53–98%) and excellent selectivities (86–96% *ee*). This asymmetric alkylation appears to be insensitive to the electronic property of the indole moiety **51** and a broad range of imine derivatives **140** can be used, including the less reactive and enolizable alkyl imines. *N*-methyl indole does not react under the same conditions suggesting that the thiourea catalyst activates the indole and the imine moieties through hydrogen bonding interactions. Interestingly, the enantiomer of catalyst **141** has also been tested in the reaction giving similar results, which shows that this methodology can be easily applied to prepare either enantiomers of the desired 3-indolyl methanamines **142**. More recently, He et al. reported the use of a thiourea supported on mesoporous silica for the same F-C alkylation with good results (66–80% yield, up to 99% *ee*).[80] The catalyst can be easily separated by filtration from the reaction mixture and reused several times without significant loss of enantioselectivity.



Scheme 36.

After proving that achiral thiourea derivatives could efficiently catalyze the F-C reaction between nitroolefins **120** and various electron-rich aromatic rings (indoles, pyrroles and anilines),[81] Ricci et al. developed in 2005 an asymmetric version of this reaction using indoles **72** as the nucleophilic substrates [Scheme 37, Equation (1)].[82] The methodology allows the isolation of the optically active 2-indolyl-1-nitro ethanes **144** in good yields (37–88%) and enantioselectivities (71–89% *ee*) with 20 mol-% of **143** incorporating a *cis*-1-amino-2-indanol as the source of chirality. As expected, better results are obtained from electron-enriched indole rings. The presence of an electron-withdrawing substituent considerably decreases the yield and moderately lowers the enantiomeric excess. The reaction appears quite general with a broad range of nitroalkenes **120** where heteroaromatic groups or aliphatic side chains are well-tolerated. A more sterically hindered isopropyl substituent has a negative impact on the yield (37%) although the selectivity remains good (81% *ee*). Noteworthy, modifications on the catalyst **143** (alcohol function removed or protected with a trimethylsilyl goup) induce a significant decrease of its catalytic performance, which suggests that the hydroxyl plays a crucial role in the activation process. The authors envisioned that their catalyst would act in a bifunctional fashion: the thiourea activates the nitroalkene through a double hydrogen bond and the indolic proton establishes another hydrogen bond with the alcohol moiety, which directs the nucleophilic attack on one face of the nitroolefin [Scheme 37, Equation (2)]. In 2006, Connon et al. synthesized a new family of thiourea catalysts (**145**) based on a binaphthyl core [Scheme 37, Equation (3)].[83] They applied their organocatalysts to the asymmetric F-C reaction between nitroolefins and *N*-substituted indole, known as less reactive than the unprotected heterocycle. The expected F-C adducts were prepared in moderate to good yields (54–98%) with modest enantioselectivities (up to 50% *ee*). More

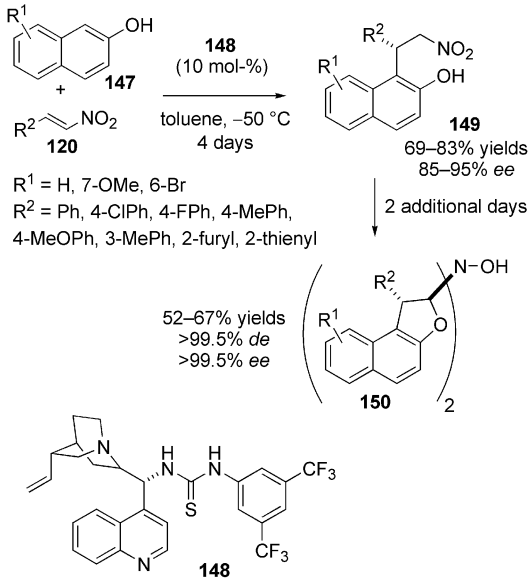
recently, Seidel et al. found that the same F-C reaction could be efficiently catalyzed by cationic thiourea derivatives **146** [Scheme 37, Equation (3)] providing the expected functionalized indoles in excellent yields (80–96%) and selectivities (90–98% *ee*).[84]



Scheme 37.

In 2008, Rozas, Connon et al. proved that epoxides could be used as electrophiles in the F-C alkylation of indole heterocycles with an *N*-sulfonyl urea catalyst.[85]

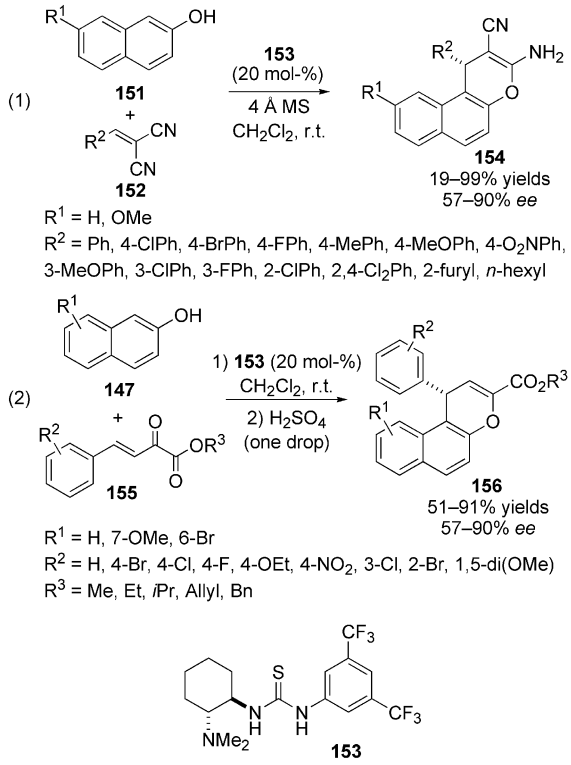
In 2007, Chen et al. investigated the use of 2-naphthols **147** as nucleophiles in the F-C reaction with nitroolefins **120** (Scheme 38).[86] With 10 mol-% of thiourea catalyst **148** derived from cinchonine, at low temperature (–50 °C), the F-C adducts **149** are synthesized in good yields (69–83%) and selectivities (85–95% *ee*). Substitution of the naphthol **147** or variations in the nature of the nitroalkene **120** appear to be tolerated in the reaction conditions. Good results are obtained in all cases although a slightly lower enantioselectivity is observed when electron-donating substituted nitrostyrenes were employed. Interestingly, when the reaction time is prolonged, an unexpected *N*-disubstituted hydroxylamine **150** begins to appear in the reaction medium and becomes the major product after 6 days. The structure of this product was confirmed by X-ray analysis. Following this pathway, different hydroxylamines **150** were prepared in moderate yields (52–67%) but very high selectivities (>99.5% *de*, > 99.5% *ee*). According to the authors, the formation of these unexpected products is also due to the thiourea catalysis and the higher enantiomeric excesses observed are the result of a kinetic resolution of the F-C adduct **149**.



Scheme 38.

Other types of electrophiles have also been used in association with 2-naphthols in F-C reactions organocatalyzed by thioureas. Yang, Zhao et al. described an enantioselective synthesis of naphthopyrans **154** starting from α,α-dicyanoolefins **152** [Scheme 39, Equation (1)].[87] The targeted pyran derivatives **154** are prepared in good yields (19–99%) and moderate enantioselectivities (57–90% *ee*) from a sequence F-C alkylation/cyclization catalyzed at room temperature by **153** incorporating a *trans*-cyclohexanediamine moiety. Although better results in terms of yields are observed with dicyanoolefins **152** substituted with electron-withdrawing groups, the nature of the substituent does not seem to affect the selectivity. Noteworthy, the authors speculated that the dicyanoolefins **152** could also be synthesized in the conditions used for the F-C alkylation. They developed a one-pot three-component (malononitrile, aldehydes and 2-naphthol **151**) synthesis of naphthopyrans **154**, which were isolated in good yields but with lower selectivities than the stepwise procedure. The same year, they also reported the synthesis of other naphthopyran derivatives **156** using β,γ-unsaturated α-keto esters **155**, following the same F-C alkylation/cyclization sequence [Scheme 39, Equation (2)].[88] Moderate to good yields (51–91%) and selectivities (57–90% *ee*) were obtained when the reaction was performed at room temperature with 20 mol-% of cata-

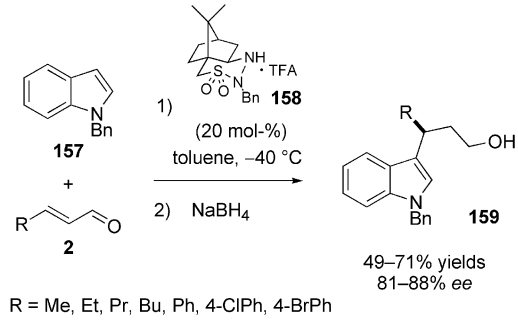
lyst loading (**153**). The addition of a catalytic amount of acid is necessary to facilitate the cyclization/dehydration step. Like in their previous work on the synthesis of naphthopyrans,[87] the procedure provided better results in the case of unsaturated α-keto esters **155** bearing electron-withdrawing substituents.



Scheme 39.

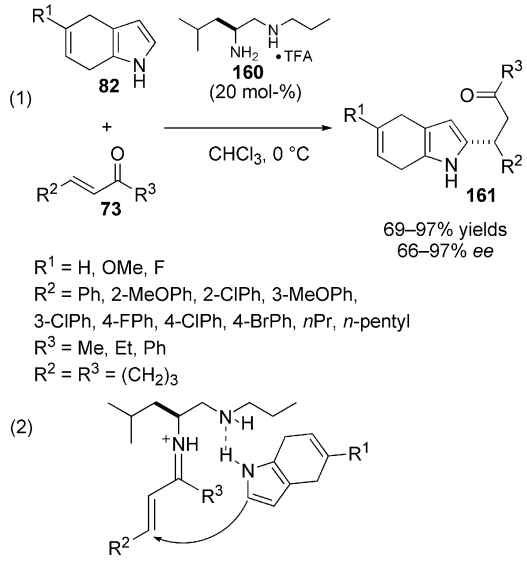
7. Other Organocatalysts

Apart from the most frequently used families of organocatalysts, other small organic molecules have proved their efficiency in catalyzing the F-C reaction. The activation of α,β-unsaturated aldehydes and ketones through LUMO-lowering by formation of an iminium intermediate has been reported with various nitrogenated heterocycles. In 2006, Xiao et al. reported that simple pyrrolidinium salts are convenient catalysts for the alkylation of indoles with α,β-unsaturated ketones providing the expected racemic adducts in excellent yields (69–92%).[89] The same year, Bonini et al. used chiral aziridin-2-yl methanols for the reaction of unsaturated aldehydes with *N*-methyl indole and pyrrole.[90] They obtained the desired alkylated heterocycles in good yields (40–85%) but moderate enantioselectivities (up to 75% *ee*). Very recently, Lee et al. described a F-C reaction catalyzed by a camphor sulfonyl hydrazine catalyst **158** (Scheme 40).[91] Performing the reaction at –40 °C in toluene, with *N*-benzyl indole **157** and a broad array of unsaturated aldehyde substrates **2**, allows to prepare the expected alcohols **159** (after reduction with $NaBH_4$) in good yields (46–71%) and selectivities (81–88% *ee*).



Scheme 40.

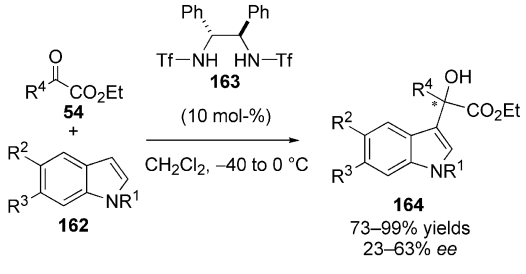
Simple 1,2-vicinal diamines derived from α-amino acids were also employed by Wang et al. for the alkylation of 4,7-dihydroindoles **82** with enones **73** [Scheme 41, Equation (1)].[92] Due to the more difficult generation of the required iminium intermediate with usual secondary amine catalysts, the authors thought that a less sterically hindered primary amine would be a more suitable choice for the activation of enones **73**. Catalyst **160** synthesized from L-leucine proved to be the more efficient of the tested diamines and enabled to isolate the 2-alkylated dihydroindoles **161** in excellent yields (69–97%) and selectivities (up to 97% *ee*) when the reaction was carried out at 0 °C in chloroform. Enones **73** bearing various aromatic or aliphatic substituents are well-tolerated in the reaction conditions, regardless of their steric or electronic properties. Substitution of the dihydroindoles **82** does not seem to affect the results either. Only the use of cyclohexenone as substrate has a detrimental effect on the selectivity (66% *ee*) although the expected adduct is isolated in excellent yield (97%). A very low reaction rate is observed in the case of *N*-protected dihydroindoles which suggests that the diamine catalyst **160** may act in a bifunctional way: the primary amine function activates the enone through the usual iminium and the secondary amine may



Scheme 41.

interact with the dihydroindole via a weak hydrogen bond directing the nucleophilic attack on one face of the double bond [Scheme 41, Equation (2)].

Activation of electrophiles through hydrogen-bonding has also been described with various types of catalysts. In 2005, Jørgensen et al. used chiral bis-sulfonyl vicinal diamines **163** to promote the F-C reaction between indoles and nitroolefins providing the expected adducts in modest to good yields (20–97%) and moderate enantioselectivities (up to 63% *ee*).[93a] They applied the same catalyst **163** to the activation of α-dicarbonyl compounds **54** in their reaction with substituted indoles **162** (Scheme 42).[93b] The F-C alkylation proceeds smoothly at low temperature (–40 to 0 °C depending on susbtrates) with 10 mol-% of catalyst **163** and provides the functionnalized indoles **164** in good yields (73–99%) but moderate selectivities (23–63% *ee*).



R^4 = H, R^1 = Me, R^3 = H, R^2 = H, OMe
R^4 = H, R^1 = Me, R^2 = H, R^3 = Cl
R^1 = R^2 = R^3 = R^4 = H
R^4 = CF_3, R^1 = Me, R^2 = R^3 = H

Scheme 42.

More recently, Xu, Xia et al. reported that camphorsulfonic acid associated with an imidazolium ionic liquid could catalyze the Michael addition of indoles on α,β-unsaturated ketones providing good yields (55–96%) but modest selectivities (up to 58% *ee*) of the expected adducts.[94] In 2007, Ramachary et al. used *N*,*N*-dimethylethanolamine, as hydrogen-bonding catalyst and cinchona alkaloid mimic, for the F-C reaction between 2-naphthols and isatins to synthesize 3-aryl-3-hydroxyindolin-2-ones in high yields (89–96%).[95]

8. Conclusion

In less than ten years since the first report on alkylation of pyrroles catalyzed by MacMillan's imidazolidinones, the organocatalyzed F-C reaction has become a powerful tool for the asymmetric functionalization of aromatic and heteroaromatic rings. Indeed, various classes of electrophiles, such as unsaturated aldehydes or ketones, imines and nitroalkenes, can be efficiently activated through either LUMO-lowering by formation of an iminium intermediate (with imidazolidinone or diarylprolinol derivatives) or generation of an electrophile-catalyst complex through hydrogen-bonding (with cinchona alkaloids, phosphoric acids or thioureas). Since the organocatalyzed F-C alkylation generally provides results (yields and enantioselectivities) comparable to metal-catalyzed reactions, it represents a complementary methodology that contributes to extend the range of procedures suitable for the asymmetric functionalization of aromatic compounds. Future efforts in this field will probably focus on broadening the scope of the reaction with regard to the nature of the aromatic nucleophiles. Indeed, most of the previously investigated examples involve indole or pyrrole derivatives and the use of simple less electron-rich benzene rings still remains challenging.

Acknowledgments

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