Copper-catalyzed reactions for organic synthesis

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Synthesis of aryl cyclopropyl sulfides through copper-promoted S-cyclopropylation of thiophenols using cyclopropylboronic acid

Emeline Benoit, Ahmed Fnaiche and Alexandre Gagnon*

Abstract
The copper-promoted S-cyclopropylation of thiophenols using cyclopropylboronic acid is reported. The procedure operates under simple conditions to afford the corresponding aryl cyclopropyl sulfides in moderate to excellent yields. The reaction tolerates substitution in ortho-, meta- and para-substitution as well as electron-donating and electron-withdrawing groups. The S-cyclopropylation of a thiophenol was also accomplished using potassium cyclopropyl trifluoroborate.

Introduction
Aryl cyclopropyl sulfides are present in many biologically active compounds, mainly in their oxidized forms. For example, aryl cyclopropyl sulfoxones have been used in the preparation of glucokinase (GK) activators for the treatment of type 2 diabetes [1-5] while aryl cyclopropyl sulfoximines have been utilized for the synthesis of modulators of glucokinase regulatory protein (GKRP) [6-8]. Roniciclib, also named BAY 1000394, is a pan-cyclin-dependant kinase (CDK) inhibitor that contains an aryl cyclopropyl sulfoximine and that was developed to treat patients with untreated small cell lung cancer [6,9].

Aryl cyclopropyl sulfides 1 are also remarkable synthons in organic synthesis (Scheme 1). For instance, the proton alpha to the sulfur can be removed by a strong base such as butyllithium, resulting in the cyclopropyllithium species 2. This carbanion can then react with alkyl halides to provide the corresponding alkylated species 3 which can then be opened up by treatment with mercuric chloride to give the corresponding β-thioaryl ketone 4 [10]. Reacting 2 with epoxides results in the formation of the 1-(β-hydroxy)cyclopropyl aryl sulfides 5 [10] while reaction with formaldehydes [11] or aldehydes [12] affords...
1-(arylthio)cyclopropylcarbinyl alcohols 6. Treating 6 with Burgess reagent or with hydrobromic acid and zinc bromide leads to 1-arylthiocyclobutanes 7 [13] and 2-alkyl-substituted cyclobutanones 8 [11,12], respectively. Treatment of 6 with hydrobromic acid and zinc bromide in the presence of a thio-phenol provides the 1,1-di(arylthio)cyclobutane 9 which, upon reaction with copper(II) triflate and Hünig’s base, rearranges to give the corresponding 2-(arylthio)-3-alkyl-1,3-butadiene 10 [12]. Reacting methyl 2-phenylthiocyclopentyl ketone 11 with silyl enol ethers 12 in the presence of dimethylaluminium chloride leads to the functionalized cyclopentanes 13 via a highly diastereoselective [3 + 2] cycloaddition reaction [14,15]. The ring expansion sequence 1 → 2 → 6 → 8 has been used as a key step in the synthesis of (±)-fragranol [16], (±)-grandisol [16], (±)-α-cuparenone [17] and (±)-herbertene [17].

Aryl cyclopropyl sulfides 1 are most frequently prepared by cyclopropylation of thiophenols 14 through $S_N2$ reaction with cyclopropyl bromide (15, Scheme 2a) [2,4] or by $S_N2$Ar reaction between aryl fluorides 16 and cyclopropanethiol (17, Scheme 2b) [6]. Although simple and attractive, these approaches usually require harsh conditions such as the presence of a strong base and high temperatures [18]. In addition, an electron-withdrawing group (EWG) must be present on the aryl fluoride 16 for the $S_N2$Ar reaction to proceed. Aryl cyclopropyl sulfides can also be accessed by the addition of thiophenols 14 to cyclopropanes 18 (Scheme 2c) [19,20] or to exo-methyleneacyclopromanes 20 (Scheme 2d) [21,22]. While these methods give access to highly substituted products, the requirement for a strong base could jeopardize their application in the context of synthesis of complex molecules. Furthermore, an electron-withdrawing group must be present on 18 to enable the Michael addition with thiol 14. Treatment of 1,3-bis(phenylthio)propanes 22 with butyllithium is another way of accessing substituted aryl cyclopropyl sulfides 23 (Scheme 2e) [23]. However, in addition to requiring a very strong base, the generation of regio- and stereoisomers from a complex starting material reduces the attractiveness of this method, particularly with respect to medicinal chemistry where expedient methods from easily accessible substrates are needed.

Organobismuth compounds are organometallic reagents that possess a C–Bi bond and which can be synthesized from inexpensive and low-toxic bismuth salts [24,25]. Due to the borderline behavior of bismuth as a metal and a ligand, organobismuth species have been used as reagents and catalysts in a wide range of reactions. We reported a portfolio of methods for the construction of C–C [26-29], C–N [30] and C–O bonds [31-33] using triaryl- and trialkylbismuthines [34]. We also disclosed for the first time in 2007 the synthesis of tricyclopolybismuth (24) and its use in N-cyclopropylation [35], palladium-catalyzed cross coupling [36] and carbonylative cross-coupling reactions [37]. Recently, we demonstrated that tricyclopolybismuth (24) can be used to S-cyclopropylate thiophenols 14, giving access to aryl cyclopropyl sulfides 1 (Scheme 2f) [38]. While this constituted the first example on the use of an organobismuth reagent in the construction of C(sp$^3$)-S bonds, synthetically, the method showed limitations such as the need for a high excess of tricyclopolybismuth (24) which transfers only one cyclopropyl unit out of three to deliver the desired products in moderate yields.

Cyclopropylboronic acid has been elegantly used by Neuville and Zhu [39,40], Tsuritani [41], Taillefer [42], Hayashi [43] and Reddy [44] as a cyclopropylating reagent in N-cyclopropylation reactions, a transformation which is similar to the Chan reaction [45], Evans [46], Lam [47] arylation reaction of N–H and O–H containing substrates. These seminal reports greatly contributed to the synthesis of cyclopropylated compounds in addition to expanding the scope of copper-catalyzed reactions in organic synthesis [48-51]. Our interest in cyclopropylation reactions led us to explore the use of cyclopropylboronic acid in the O-cyclopropylation of phenols. Unfortunately, efficient conditions could not be identified to perform this seemingly simple extension of the N-cyclopropylation reaction. Very recently, Engle and McAuliffe disclosed a solution to this problem by developing a highly efficient protocol for the direct O-cyclopropylation of phenols using potassium cyclopropyl trifluoroborate [52]. Surprisingly, and to the best of our knowledge, cyclo-
propylboronic acid or its various ester and potassium trifluoroborate derivatives have never been used in S-cyclopropylation reactions. In light of the relevance of aryl cyclopropyl sulfides in medicinal and synthetic organic chemistry, we initiated a program to explore the use of cyclopropylboronic acid (25) as an S-cyclopropylating agent of thiophenols (Scheme 2g). The publication of copper-catalyzed methods by Feng and Xu to S-arylate thiophenols [53] and by Guy to S-arylate alkyl thiols [54] gave us confidence to proceed ahead with our endeavor for which we herein report our results.

Results and Discussion

We began by testing the feasibility of S-cyclopropylating 4-tert-butylbenzenethiol (14a) with cyclopropylboronic acid (25) using reaction conditions developed by Neuville and Zhu for the N-cyclopropylation of anilines and amines [39]. Treating thiophenol 14a with 2.0 equivalents of cyclopropylboronic acid (25), 1.0 equivalent of copper(II) acetate, 1.0 equivalent of bipyridine, and 2.0 equivalents of sodium carbonate in dichloroethane at 70 °C for 16 hours provided the desired S-cyclopropylated compound 1a in 86% yield accompanied by only 4% of the diaryl disulfide side-product 26a (Table 1, entry 1, "standard conditions"). Reducing the catalyst loading by a factor of two under oxygen atmosphere led to a dramatic reduction in the yield of the reaction (Table 1, entry 2). Performing the reaction under oxygen with a stoichiometric amount of copper(II) acetate also proved unsuccessful and afforded mainly the disulfide product, suggesting a deleterious effect of oxygen (Table 1, entry 3). Yet, to our surprise, performing the reaction under argon also negatively impacted the yield of the reaction (Table 1, entry 4), showing that air is the ideal (and also most convenient) atmosphere for this reaction. Changing the solvent for toluene, dichloromethane, dimethylformamide or DMF/H2O (4:1) led to lower yields of the desired aryl cyclopropyl sulfide.
Table 1: Optimization of the reaction conditions for the copper-promoted S-cyclopropylation of thiophenol 14a with boron-based cyclopropylating reagents.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Change from &quot;standard conditions&quot;</th>
<th>Yield 1a (%)b</th>
<th>Yield 26a (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>no changea</td>
<td>86</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>0.5 equiv of Cu(OAc)_2 instead of 1.0 equiv under O_2 instead of air</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>O_2 instead of air</td>
<td>19</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>argon instead of air</td>
<td>45</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>toluene, DCM, DMF or DMF/H_2O (4:1) instead of DCE</td>
<td>&lt;40</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>50 °C instead of 70 °C</td>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>7</td>
<td>1,10-phenanthroline instead of bipy</td>
<td>81</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>1.5 equiv of cPrB(OH)_2 (25) instead of 2.0 and 1.0 equiv of Na_2CO_3</td>
<td>85</td>
<td>14</td>
</tr>
<tr>
<td>9</td>
<td>1.5 equiv of cPrB(OH)_2 (25) instead of 2.0 and 1.0 equiv of Cs_2CO_3 instead of 2.0 equiv of Na_2CO_3</td>
<td>92</td>
<td>6</td>
</tr>
<tr>
<td>10</td>
<td>1.5 equiv of cPrB(OH)_2 (25) instead of 2.0, 1.0 equiv of Cs_2CO_3 instead of 2.0 equiv of Na_2CO_3 and 6 h instead of 16 h</td>
<td>85</td>
<td>14</td>
</tr>
<tr>
<td>11</td>
<td>27 instead of cPrB(OH)_2 (25)</td>
<td>0</td>
<td>85c</td>
</tr>
<tr>
<td>12</td>
<td>28 instead of cPrB(OH)_2 (25)</td>
<td>0</td>
<td>96c</td>
</tr>
<tr>
<td>13</td>
<td>29 instead of cPrB(OH)_2 (25)</td>
<td>23</td>
<td>30</td>
</tr>
</tbody>
</table>

aStandard conditions: 4-tert-butybenzenethiol (14a, 1.0 equiv), cyclopropylboronic acid (25, 2.0 equiv), Cu(OAc)_2 (1.0 equiv), bipyridine (1.0 equiv), Na_2CO_3 (2.0 equiv), dichloroethane (0.1 M), 70 °C, 16 h, air. bYields of isolated pure products. cConversion calculated by NMR.

1a (Table 1, entry 5) while decreasing the temperature to 50 °C almost completely shut down the reaction (Table 1, entry 6). 1,10-Phenanthroline was found to be the only viable alternative to bipyridine (Table 1, entry 7), with other ligands commonly used in copper-catalyzed reactions such as proline and 2,2,6,6-tetramethyl-3,5-heptanedione giving yields under 15%. Reducing the number of equivalents of boronic acid 25 and sodium carbonate was found to be well tolerated, giving a comparable yield as the "standard conditions" (Table 1, entry 8). While changing the inorganic base to potassium phosphate tribasic or potassium carbonate gave yields below 75%, we found that cesium carbonate provided a net increase in the yield of the reaction (Table 1, entry 9). Attempts at reducing the reaction time led to a minor erosion in the yield of the reaction (Table 1, entry 10). Replacing cyclopropylboronic acid (25) with cyclopropylboronic acid pinacol ester (27) or cyclopropylboronic acid MIDA ester 28 afforded 85% and 96% of the corresponding diaryl disulfide 26a, respectively, with no observable traces of the desired S-cyclopropylated product 1a (Table 1, entries 11 and 12). Interestingly, however, potassium cyclopropyl trifluoroborate (29) provided the desired aryl cyclopropyl sulfide 1a in 23% yield, albeit with 30% of the diaryl disulfide side-product 26a (Table 1, entry 13). Although encouraging, it was clear that the S-cyclopropylation with cPrBF_3K (29) would necessitate extensive optimization and therefore, we decided to pursue our work with cPrB(OH)_2 (25).

With our optimized reaction conditions in hand (i.e., Table 1, entry 9), we embarked on exploring the scope of the copper-promoted S-cyclopropylation of thiophenols using cyclopropylboronic acid (25, Scheme 3). Our studies showed that the reaction can be performed on unsubstituted benzenethiol as well as on para- and meta-methylbenzenethiols, affording the corresponding products 1b–d in 84 to 99% yield. Substitution of the aryl ring at the ortho-position resulted in a considerable drop in the efficiency of the process, as indicated by compound 1e.
which was obtained in a moderate 57% yield. In line with those results, cyclopropyl(3,5-dimethylphenyl)sulfane (1f) was obtained in 76% yield while the 2,4-isomer 1g was produced in a low 31% yield. Electron-withdrawing groups such as a fluorine, bromine, chlorine, trifluoromethyl and a nitro group as well as electron-donating groups such as a methoxy group at the para-position were found to be well tolerated, as indicated by aryl cyclopropyl sulfides 1h–m which were obtained in yields ranging from 72 to 95%. Moving the bromine from the para- to the meta-position resulted in a substantial reduction in the yield of the reaction, as shown by compound 1n. Compound 1o possessing a methyl ester at the ortho-position was prepared in 44%, a yield which is consistent with the one obtained for the ortho-methyl product 1e. Compound 1o indicates some level of tolerance towards functional groups that can be used à posteriori to modify the product. Diaryl disulfides 26 were isolated in yields ranging from 2 to 36%, depending on the thiophenol. Attempts at S-cyclopropylating benzyl mercaptan, an alkylthiol, failed to deliver the desired product.

Engle and McAlpine recently reported a very efficient, simple and general protocol for the O-cyclopropylation of phenols using potassium cyclopropyl trifluoroborate (29) that leads to the corresponding aryl cyclopropyl ethers in good to excellent yields [52]. We wanted to study the transposibility of these conditions to the S-cyclopropylation of thiophenols. In the event, treating 4-tert-butylbenzenethiol (14a) with 3.0 equivalents of potassium cyclopropyl trifluoroborate (29) in the presence of 0.1 equivalents of copper(II) acetate, 0.1 equivalents of 1,10-phenanthroline, 2.0 equivalents of potassium carbonate under oxygen atmosphere at 70 °C for 20 hours in a 3:1 mixture of toluene and water afforded the aryl cyclopropyl sulfide 1a in 38% along with 8% of the corresponding side-product 26a and 24% of recovered starting material 14a (Scheme 4). These results are encouraging and demonstrate that the Engle/McAlpine conditions are applicable, to some extent, to the S-cyclopropylation of thiophenols. It is reasonable to believe that thorough optimization of the reaction conditions should result in a more efficient process. Efforts towards this goal are in progress in our laboratory and results will be reported in due course.

Conclusion

In conclusion, we developed a simple protocol for the S-cyclopropylation of thiophenols using cyclopropylboronic acid. The reaction is promoted by copper(II) acetate and tolerates electron-withdrawing and electron-donating groups at the ortho-, meta-, and para-positions of the aryl ring to afford the corre-
responding aryl cyclopropyl sulfides in moderate to excellent yields. This protocol provides an efficient alternative to our previously reported method for the S-cyclopropylation of thiophenols using tricyclopropylbismuth.

Experimental

General information

Unless otherwise indicated, all reactions were run under argon in flame-dried glassware. Commercial reagents were used without further purification. Cu(OAc)₂ (97%) was purchased from Strem Chemicals. Anhydrous solvents were obtained using an encapsulated solvent purification system and were further dried over 4 Å molecular sieves. The evolution of reactions was monitored by analytical thin-layer chromatography using silica gel 60 F254 precoated plates. Flash chromatography was performed employing 230–400 mesh silica using the indicated solvent system according to standard techniques. Proton nuclear magnetic resonance spectra were recorded on 300 or 600 MHz spectrometers. Chemical shifts for ¹H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform, δ 7.26 ppm). Data is reported as follows: chemical shift δ, multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublet, ddd = doublet of doublet of doublet, td = triplet of doublet, m = multiplet), coupling constant J in Hz and integration. Melting points are uncorrected.

General procedure for the synthesis of aryl cyclopropyl sulfides

A sealed tube equipped with a magnetic stirring bar was charged under ambient air with cyclopropylboronic acid (25, 0.6 mmol, 1.5 equiv), cesium carbonate (0.4 mmol, 1.0 equiv), Cu(OAc)₂ (0.4 mmol, 1.0 equiv), 2,2'-bipyridine (0.4 mmol, 1.0 equiv) and thiophenol 14 (0.4 mmol, 1.0 equiv). Dichloroethane (0.1 M) was added, the tube was sealed and heated at 70 °C for 16 hours. The reaction mixture was cooled to room temperature and aqueous NH₄OH 25% (5 mL) was added. The reaction mixture was stirred for a few minutes, transferred in a separatory funnel and extracted with DCM (3 × 5 mL). The combined organic layers were washed with brine (2 × 10 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was purified by flash column chromatography using the indicated solvent system to afford the corresponding aryl cyclopropyl sulfide 1 and diaryl disulfide 26 as a side-product.

(4-(tert-Butyl)phenyl)(cyclopropyl)sulfane (1a) and 1,2-bis(4-(tert-butyl)phenyl)disulfane (26a). The general procedure was followed on 0.425 mmol scale starting from 4-(tert-butyl)benzenethiol (14a). The residue was purified on silica gel (100% Hex) to afford 1a (80.4 mg, 92%) and 26a (4.2 mg, 6%) as a colorless oil and a white solid, respectively. 1a: Spectral data was identical to literature compound [38]. ¹H NMR (300 MHz, CDCl₃) δ 7.33 (s, 4H), 2.23–2.16 (m, 1H), 1.33 (s, 9H), 1.08–1.02 (m, 2H), 0.73–0.68 (m, 2H). 26a: mp 65.0–68.5 °C. Spectral data was identical to literature compound [55]. ¹H NMR (300 MHz, CDCl₃) δ 7.44 (d, J = 8.7 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 1.30 (s, 9H).

Cyclopropyl(phenyl)sulfane (1b). The general procedure was followed on 0.400 mmol scale starting from benzenethiol (14b). The residue was purified on silica gel (100% Hex) to afford 1b (59.2 mg, 99%) as a slightly yellow oil; Spectral data was identical to literature compound [38]. ¹H NMR (300 MHz, CDCl₃) δ 7.39–7.35 (m, 2H), 7.32–7.28 (m, 1H), 7.17–7.11 (m, 1H), 2.23–2.15 (tt, J = 8.4, 1.2 Hz, 1H), 1.10–1.04 (m, 2H), 0.72–0.62 (m, 2H).

Cyclopropyl(p-tolyl)sulfane (1c). The general procedure was followed on 0.400 mmol scale starting from 4-methylbenzenethiol (14c). The residue was purified on silica gel (100% Hex) to afford 1c (61.8 mg, 94%) as a colorless oil: Spectral data was identical to literature compound [38]. ¹H NMR (300 MHz, CDCl₃) δ 7.44 (d, J = 3.9 Hz, 2H), 7.12 (d, J = 4.2 Hz, 2H), 2.33 (s, 3H), 2.22–2.18 (m, 1H), 1.06–1.03 (m, 2H), 0.71–0.68 (m, 2H).

Cyclopropyl(m-tolyl)sulfane (1d) and 1,2-di(m-tolyl)disulfane (26d). The general procedure was followed on 0.400 mmol scale starting from 3-methylbenzenethiol (14d). The residue was purified on silica gel (100% Hex) to afford 1d (55.2 mg, 84%) and 26d (6.9 mg, 14%) as a colorless and a yellow oil, re-

![Scheme 4: Copper-catalyzed S-cyclopropylation of 4-tert-butylbenzenethiol (14a) using potassium cyclopropyl trifluoroborate (29).](image-url)
spectively. 1d: Spectral data was identical to literature compound [38]. 1H NMR (300 MHz, CDCl₃) δ 7.19–7.18 (m, 3H), 6.97–6.94 (m, 1H), 2.34 (s, 3H), 2.23–2.15 (m, 1H), 1.09–1.03 (m, 2H), 0.72–0.67 (m, 2H). 26d: Spectral data was identical to literature compound [56]. 1H NMR (300 MHz, CDCl₃) δ 7.32 (s, 2H), 7.30 (d, J = 3.9 Hz, 2H), 7.19 (t, J = 8.0 Hz, 2H), 7.03 (d, J = 7.5 Hz, 2H), 2.32 (s, 6H).

Cyclopropyl(o-toly)sulfane (1e) and 1,2-di(o-toly)disulfane (26e). The general procedure was followed on 0.400 mmol scale starting from 3,5-dimethylbenzenethiol (14e). The residue was purified on silica gel (100% Hex) to afford 1e (37.5 mg, 57%) and 26e (7.9 mg, 16%) as a slightly yellow and a yellow oil, respectively. 1f: Spectral data was identical to literature compound [38]. 1H NMR (300 MHz, CDCl₃) δ 7.43 (d, J = 3.9 Hz, 2H), 7.41 (d, J = 9.0 Hz, 2H), 2.27 (s, 3H), 2.17–2.09 (m, 1H), 1.13–1.07 (m, 2H), 0.73–0.67 (m, 2H). 26f: Spectral data was identical to literature compound [57]. 1H NMR (300 MHz, CDCl₃) δ 7.52–7.49 (m, 2H), 7.47–7.43 (m, 2H), 7.34 (d, J = 8.4 Hz, 4H), 7.30–7.22 (m, 4H), 2.20–2.12 (m, 1H), 1.10–1.03 (m, 2H), 0.70–0.65 (m, 2H). 26j: mp 71.0–73.0 °C. Spectral data was identical to literature compound [58]. 1H NMR (300 MHz, CDCl₃) δ 7.12 (s, 4H), 6.85 (s, 2H), 2.28 (s, 12H).

Cyclopropyl(3,5-dimethylphenyl)sulfane (1f) and 1,2-bis(3,5-dimethylphenyl)disulfane (26f). The general procedure was followed on 0.400 mmol scale starting from 3,5-dimethylbenzenethiol (14f). The residue was purified on silica gel (100% Hex) to afford 1f (54.2 mg, 76%) and 26f (13.2 mg, 24%) as a colorless and a yellow oil, respectively. 1f: Spectral data was identical to literature compound [38]. 1H NMR (300 MHz, CDCl₃) δ 7.53 (d, J = 7.5 Hz, 2H), 2.32 (s, 6H).

Methyl 2-(cyclopropylthio)benzoate (1o) and dimethyl 2,2'-disulfanediyldibenzoate (26o). The general procedure was followed on 0.484 mmol scale starting from 3-bromobenzenethiol (14m). The residue was purified on silica gel (100% Hex) to afford 1o (24.1 mg, 36%) as a yellow oil and a white solid, respectively. 

Supporting Information

Supporting Information File 1
Copies of NMR spectra of synthesized compounds.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-15-113-S1.pdf]

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Combination of multicomponent KA\textsuperscript{2} and Pauson–Khand reactions: short synthesis of spirocyclic pyrrolocyclopentenones

Riccardo Innocenti\textsuperscript{1}, Elena Lenci\textsuperscript{1}, Gloria Menchi\textsuperscript{1} and Andrea Trabocchi\textsuperscript{*1,2}

Abstract

The Cu-catalyzed multicomponent ketone–amine–alkyne (KA\textsuperscript{2}) reaction was combined with a Pauson–Khand cycloaddition to give access of unprecedented constrained spirocyclic pyrrolocyclopentenone derivatives following a DOS couple-pair approach. The polyfunctional molecular scaffolds were tested on the cyclopentenone reactivity to further expand the skeletal diversity, demonstrating the utility of this combined approach in generating novel spiro compounds as starting material for the generation of chemical libraries. The chemoinformatics characterization of the newly-synthesized molecules gave evidence about structural and physicochemical properties with respect to a set of blockbuster drugs, and showed that such scaffolds are drug-like but more spherical and three-dimensional in character than the drugs.

Introduction

The screening of small molecule libraries is a well-established approach in early-stage drug discovery to identify hit candidates for the development of drug leads. The application of unconventional molecular scaffolds to develop chemical libraries can increase the chance of finding compounds able to address the so-called “undruggable” targets, such as protein–protein interactions [1]. In this context, molecules containing one or more rings are of primary interest, as they will suffer a reduced conformational entropy penalty upon binding to a protein target, and the approach of constraining the ligand conformation with a ring is widely used in drug design [2]. Accordingly, with increasing interest for sp\textsuperscript{3}-rich molecules, spirocyclic compounds are being considered valuable as molecular platforms for the generation of high-quality small molecule
collections, taking advantage of the stereochemical diversity, and of their three-dimensional shape and structural bias to develop lead compounds, specifically in the field of protein–protein interactions [3-6]. Spiranic rings such as spiroketalas are present in numerous natural products [7-9], a wide array of spirocyclic compounds are being studied in drug discovery and their chemical space have been systematically charted and characterized recently by Bajorath and co-workers (Figure 1) [10]. This study revealed that spirocycles are found only in few approved drugs [11] and that there is a significant potential to explore the chemical space of spirocyclic scaffolds, especially in the case of the condensed ones. Thus, new synthetic routes towards the synthesis of building blocks containing spiranic rings have increasingly appeared in the recent literature [12].

Among the synthetic approaches to improve the quality and quantity of small molecules members of chemical libraries, diversity-oriented synthesis (DOS) [13-16], has been proposed as a paradigm for developing large collections of structurally diverse small molecules in a way to generate the maximum diversity and complexity from simple starting materials applying divergent synthetic strategies, such as the use of complexity-generating reactions and the build/couple/pair approach [17,18]. The application of multicomponent approaches has proven to be very useful as starting points in DOS [19-22], such as the exploitation of the Petasis three-component [23-29] and the Ugi four-component reactions [30-33], showing interesting properties for the generation of compounds characterized by high stereochemical and skeletal diversity. Although not fully exploited so far, some contributions on the diversity-oriented synthesis of spirocyclic compounds have appeared in the literature recently, also employing multicomponent approaches to give the spirocyclic adduct after a cyclization step [34-36]. We recently focused our interest to the cyclopentenone ring [37], as this heterocycle is a powerful synthons for the synthesis of a variety of bioactive target molecules, due to the broad diversity of chemical modifications available for the enone structural motif [38]. The most common approach to access such chemotype is the Pauson–Khand (PK) reaction [39,40], consisting of a $[2 + 2 + 1]$ cycloaddition between an olefin, alkyne, and carbon monoxide. This reaction has been also applied in cascade approaches [41], and in combination with RCM [42], Diels–Alder [43] and Staudinger [44] reactions to produce novel structurally complex chemical entities. Following our interest to DOS as a synthetic strategy for the generation of molecular scaffolds according to a couple/pair approach [45-47], we reasoned to combine the copper-catalyzed ketone–amine–alkyne (KA$_2$) multicomponent coupling reaction [48] with the Pauson–Khand cycloaddition as the pairing reaction to achieve spirocyclic pyrrolocyclopentenone derivatives. Specifically, the KA$_2$ reaction was envisaged taking into account cyclic ketones, to install a quaternary carbon atom carrying the required 1,6-enzyme moiety for the subsequent Pauson–Khand reaction, thus achieving the corresponding tricyclic structure in three single steps (Scheme 1b). This unprecedent molecular scaffold repre-

![Figure 1: Chemical structure of representative approved drugs containing a spirocyclic moiety.](image-url)
Scheme 1: Synthetic strategies for accessing pyrrolocyclopentenone derivatives, including the novel couple/pair approach that combines the KA² and PK multicomponent reactions. L.A. = Lewis acid; PK = Pauson–Khand.

Results and Discussion

Cyclohexanone (1) and phenylacetylene (2) were taken into account for the optimization of the KA² reaction conditions with allylamine, in order to attain a quaternary carbon atom containing suitable alkenyl and alkynyl appendages for subsequent Pauson–Khand intramolecular cycloaddition (Scheme 2).

The KA² reaction was assayed following the reported method [48] employing copper catalysis, and tested on our starting material upon variation of copper salts, solvents and temperature, resulting in the neat reaction under Cul catalysis being optimal when carried out for 2 h at 100 °C under microwave irradiation (Scheme 2).

(see Supporting Information File 1), as it can promote metal-catalyzed reactions [53]. The scope of the combined approach employing KA² and Pauson–Khand reactions was studied by varying the alkyne and ketone components, along with the
acylating moiety being installed before the Pauson–Khand reaction (Scheme 2 and Table 1). The acylation of the amino group was found necessary to allow for the cobalt-catalyzed reaction to proceed under a CO atmosphere. This step was also carried out in one pot after the KA² reaction by diluting with pyridine and adding the acylating reagent, to achieve the corresponding product in slightly lower yield. Attempts to carry out the Pauson–Khand reaction directly on the amino group before the acylation step did not work, nor using a modified approach using ammonium chloride and 1.5 equivalents of Co₃(CO)₈.

Table 1: Scope of the combined KA² and Pauson–Khand multicomponent processes.⁴

<table>
<thead>
<tr>
<th>entry</th>
<th>ketone</th>
<th>alkyne</th>
<th>yield, %</th>
<th>PK product</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>KA² product</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>Ph</td>
<td>2</td>
<td>3: R = H, 82%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4: R = Ac, 61%</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td></td>
<td>6</td>
<td>7: R = H, 74%</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>8: R = Ac, 78%</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td></td>
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<td>13: R = H, 61%</td>
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<td>14: R = Ac, 56%</td>
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<tr>
<td>6</td>
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<td>17: R = H, 82%</td>
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<td></td>
<td>18: R = Ac, 68%</td>
</tr>
<tr>
<td>7</td>
<td>20</td>
<td>2</td>
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</tbody>
</table>

⁴ The acylating moiety was installed before the Pauson–Khand reaction (Scheme 2 and Table 1). The acylation of the amino group was found necessary to allow for the cobalt-catalyzed reaction to proceed under a CO atmosphere. This step was also carried out in one pot after the KA² reaction by diluting with pyridine.
Table 1: Scope of the combined KA\textsubscript{2} and Pauson–Khand multicomponent processes.\textsuperscript{a} (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Structure</th>
<th>Reaction Conditions</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td><img src="image1" alt="structure" /></td>
<td>KA\textsubscript{2} reaction: ketone (1 equiv), alkyne (1.2 equiv) and amine (1.2 equiv), CuI (0.2 equiv), 100 °C, 2 h, microwave irradiation. Amine protection: pyridine (2 mL/mmol), acetic anhydride (4 mL/mmol), 40 °C, 16 h.</td>
<td><img src="image2" alt="structure" /></td>
<td><img src="image3" alt="structure" /></td>
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<tr>
<td>9</td>
<td><img src="image4" alt="structure" /></td>
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<td><img src="image5" alt="structure" /></td>
<td><img src="image6" alt="structure" /></td>
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<td>10</td>
<td><img src="image7" alt="structure" /></td>
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<td><img src="image8" alt="structure" /></td>
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<td>11</td>
<td><img src="image10" alt="structure" /></td>
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<td></td>
<td><img src="image20" alt="structure" /></td>
<td><img src="image21" alt="structure" /></td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction conditions. KA\textsubscript{2} reaction: ketone (1 equiv), alkyne (1.2 equiv) and amine (1.2 equiv), CuI (0.2 equiv), 100 °C, 2 h, microwave irradiation. Amine protection: pyridine (2 mL/mmol), acetic anhydride (4 mL/mmol), 40 °C, 16 h. Pauson–Khand reaction: enyne (1 equiv), Co\textsubscript{2}(CO)\textsubscript{8} (0.1 equiv), N,N,N',N'-tetramethylthiourea (0.6 equiv), toluene (20 mL/mmol), CO atmosphere, 70 °C, 3–8 h.
under an inert atmosphere, as reported for similar reactions in the presence of basic nitrogen atoms [28].

The variation of the alkyne component proved to give the KA² coupling adduct when aromatic terminal alkynes were used, as shown in Table 1, entries 1 and 2 for those containing phenyl and thienyl moieties, resulting in 82% and 74% yield for the KA² step. Subsequent acylation and pairing steps proved to proceed in good yield, thus furnishing the corresponding spirocyclopentenone derivatives 5 and 9 with an aromatic appendage at the carbonyl alpha carbon. On the contrary, when aliphatic alkynes were applied in the KA² process, no reaction with allylamine and cyclohexanone was achieved, suggesting a role of the aromatic ring in activating the alkyne towards the copper-catalyzed process (Table 1, entries 3 and 4), as previously reported in other works [54]. Use of cyclopentanone, thus varying the ring size of the cyclic ketone, resulted in the conversion to the title spirocyclopentenone derivative, although in slightly lower yield as compared for the homologous ketone (Table 1, entry 5). No conversion to the KA² adduct was achieved by using unsaturated or aromatic ketones (Table 1, entries 7 and 8, respectively), confirming an important role of the electronic content of the components in the outcome of the multicomponent coupling reaction. Similarly, the use of piperidone as the ketone component proved to work only when the amino group was protected as Boc, whereas the N-methyl derivative did not proceed to the coupling product (Table 1, entries 10 and 9, respectively). Indeed, the Boc-piperidone furnished the corresponding spirocyclopentenone derivatives upon changing both the aromatic alkyne or the acylating agent (Table 1, entries 10–12). When the Boc group was replaced with the tosyl one as the N-substituent, such chemical moiety proved to impair the subsequent Pauson–Khand reaction (Table 1, entry 13), possibly due to a coordinating effect towards the cobalt catalyst. Such an effect was confirmed when the N-tosylpiperidone was used as the ketone component, as also in this case the presence of the tosyl group impaired the acetylated KA² adduct from reacting under Pauson–Khand conditions (Table 1, entry 14).

The synthetic utility of the spiro derivatives resulting from the combined KA²/Pauson–Khand process to generate second-generation molecular scaffolds was tested on compound 5 by applying representative reactions on the enone structural motif (Scheme 3).

The chemoselective carbonyl reduction to obtain the corresponding allylic alcohol derivative 36 was achieved in 92% under Luche reduction conditions employing NaBH₄/CeCl₃ in MeOH/DCM, resulting in the selective synthesis of the syn-alcohol, as a consequence of the formation of the equatorial alcohol favored by reduced gauche interactions [55]. Subsequent epoxidation at the double bond directed by the hydroxy group and using m-chloroperbenzoic acid allowed to install two additional stereocenters with complete control of the relative stereochemistry in 68% yield. Such two-step synthesis proved to proceed also in one-pot, resulting in the generation of the stereochemically dense epoxyalcohol 37 in 68% overall yield. The treatment of compound 5 with EtMgBr as a Grignard

Scheme 3: Follow-up chemistry on compound 5 taking advantage of the enone chemistry. Reaction conditions. (i) NaBH₄ (2 equiv), CeCl₃/7H₂O (2 equiv), DMC/MeOH 1:1 (20 mL/mmol), 25 °C, 1 h; (ii) m-CPBA (1 equiv), DCM (6.5 mL/mmol), 0 °C, 4 h; (iii) EtMgBr 3 M in Et₂O (5 equiv), CeCl₃ (1 equiv), THF (6 mL/mmol), 0 °C, 30 min; (iv) NaN₃ (1.8 equiv), TFA (5 mL/mmol), reflux, 16 h.
reagent in the presence of CeCl$_3$ gave the corresponding tertiary alcohol 38 with similar stereochemical features as of 36 in the formation of the equatorial alcohol, although in lower yield. The use of CeCl$_3$ together with EtMgBr was found particularly effective to suppress conjugate additions, with similar yield as reported for analogous substrates [56]. Subsequent acid-catalyzed displacement of the hydroxy moiety with aniline in the presence of camphorsulfonic acid did not give the desired amine, supporting the hypothesis of steric hindrance at such position [57]. Similarly, Simmons–Smith cyclopropanation reaction [58] did not work, and so as for the cycloaddition reaction with Danishefsky’s diene, possibly due to steric hindrance imposed by the adjacent phenyl and cyclohexyl rings [59]. The treatment of compound 5 under Schmidt reaction conditions with sodium azide in TFA [60] resulted in the conversion to the corresponding six-membered ring lactam 39 in 41% yield, demonstrating the reactivity of the enone 5 at the carbonyl group and showing stability towards harsh acidic conditions.

The structural assignment of compound 36 was assessed by detailed 1D and 2D NMR studies, and corroborated with molecular modeling calculations. NOESY-1D experiments carried out with a mixing time of 500 ms allowed to identify the unique rotamer possessing a Z geometry, as evinced by a NOE interaction between H$_d$ and the methyl group. The cis relationship between the OH group and the pyrrolidine ring, resulting from the chemo- and stereoselective syn reduction of the carbonyl group, was evinced by NOESY-1D experiments showing intense NOE effects between H$_c$ and H$_a$ protons, as also shown in NOESY 2D spectrum (see Figure 2 and Supporting Information File 1). A similar analysis allowed the structural assignment for 38.

### Chemoinformatic analysis

The structural features of the compounds so obtained and representative functionalized molecular scaffolds were analyzed in terms of chemical properties and shape analysis in the context of the chemical space [61] using principal component analysis (PCA) and principal moments of inertia (PMI) analysis. PCA is a statistical tool to condense multidimensional chemical properties (i.e., molecular weight, logP, ring complexity) into single dimensional numerical values (principal components), to simplify the comparison with different sets of compounds. ChemGPS-NP [62-64] was chosen for the PCA analysis, providing a comprehensive exploration of the chemical space in terms of global mapping onto a consistent 8-dimensional map of structural characteristics [65]. In particular, the first and the second dimensions (PC1 and PC2) are the most interesting ones, being associated respectively with size, shape, and polarizability and with aromatic and conjugation related properties. The analysis of PC1 vs PC2 of compounds 3–39, in comparison with a reference set of 40 brand-name blockbuster drugs [66,67] (Figure 3), showed the different distribution of compounds 3–39 in two different clusters. Most of the compounds reside in the first cluster, positioned in the negative direction of x axis, in a region that shows good overlap with drugs like levaquin, which is characterized by a complex tricyclic skeleton. The addition of a second aromatic ring, as the benzoyl or tosyl group of compounds 30–32, 34 and 35, increased the aromatic- and conjugation-related character of the structure, thus resulting in shifting those compounds to a second cluster being positioned in the positive direction for both axes, together with drugs possessing large aromatic content, as benazepril and serquel.

The principal moments of inertia (PMI) analysis was also taken into account for the three-dimensional shape analysis of compounds 3–39 in the context of chemical space, again with reference to a set of BB drugs. The three principal moments of inertia ($I_{xx}$, $I_{yy}$, $I_{zz}$) and the corresponding normalized principal moments of inertia were determined according to Sauer and Schwarz [68] for the lowest energy conformation of all the compounds and the reference drugs. Then, the normalized PMI ratios were plotted on a triangular graph where the vertices (0,1), (0.5,0.5), and (1,1) represent a perfect rod (i.e., 2-butyne), disc (i.e., benzene), and sphere (i.e., adamantane), respectively (Figure 4). This analysis showed that all compounds 3–39 pos-
Figure 3: PCA plot resulting from the correlation between PC1 vs PC2, showing the positioning in the chemical space of compounds 3–39 (blue diamonds) with respect to the reference set of brand-name blockbuster drugs (orange squares).

Figure 4: PMI plot showing the skeletal diversity of compounds 3–39 (blue diamonds) with respect to the reference set of brand-name blockbuster drugs (orange squares).
ess lower tendency to stay in the rod side of the triangle, as compared to BB drugs, suggesting for these compounds a higher shape complexity, as due to the presence of quaternary carbon atoms introduced by the KA² coupling reaction. The intramolecular Pauson–Khand cyclization proved to be even more efficient in increasing the three-dimensional character of these compounds, as spiro tricyclic products were found to be more shifted towards the sphere-disc region of this chemical space, especially if compared to their corresponding starting materials (see Figure 4, compounds 5 and 26 with respect to 3 and 24, respectively). This feature is promising in view of expanding the array of molecular scaffolds of this nature for drug discovery purpose, as a higher scaffold complexity is generally associated with a more successful outcome in drug discovery and development [69–71]. On the other hand, the reduction of the carbonyl group into an alcohol was not significant in increasing the three-dimensional character of the structure, as compounds 36–38 were found to be more shifted towards the rod-sphere axes as compared to the parent compound 5.

Conclusion

Spirocyclic compounds are valuable molecular platforms for the generation of high-quality small molecule collections, taking advantage of their three-dimensional shape and structural bias to develop lead compounds. The combination of multicomponent KA² and Pauson–Khand reactions using representative cyclic ketones, allylamine and phenylacetylene gave access to highly constrained spirocyclopentenone derivatives following a DOS couple-pair approach. A representative spirocyclopentenone derivative was applied to follow-up chemistry employing the enyne reactivity to further expand the skeletal diversity, resulting in additional chemotypes useful as starting compounds for appendage diversity in the generation of chemical libraries. The chemoinformatics characterization of the newly-synthesized molecules gave evidence about structural and physicochemical properties with respect to a set of blockbuster drugs, and showed that such scaffolds are drug-like but more spherical and three-dimensional in character than the drugs. These combined approaches are being applied in chemistry as more efficient synthetic approaches to expand the array of polyfunctional sp³-rich molecular scaffolds in the effort of increasing the synthetically-accessible chemical space.

Experimental

General procedure (A) for the KA² coupling reaction. Cul (0.2 equiv) was added in a dry sealed vial for microwave synthesis under a nitrogen flow. Then, ketone (1 equiv), alkyne (1.2 equiv) and amine (1.2 equiv) were successively added under a nitrogen flow, and the mixture was heated under microwave irradiation to 100 °C for 2 h. Then, EtOAc was added and the organic phase was washed with 5% NH₄OH (3 × 20 mL) and brine. The organic phase was dried with Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by flash chromatography using the indicated solvent mixture as eluent.

General procedure (B) for the amine protection. The KA² product was dissolved in pyridine (2 mL/mmol) and acetic anhydride (4 mL/mmol) was added dropwise to the reaction mixture at 0 °C. Then, the reaction mixture was heated to 40 °C for 16 h, followed by EtOAc addition. The organic phase was washed with 1 M HCl (3 × 20 mL), satd. Na₂CO₃ (3 × 20 mL) and brine. The organic phase was dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by flash chromatography using the indicated solvent mixture as eluent.

General procedure for the Pauson–Khand (C) reaction. In a dry round bottom flask under a nitrogen flow Co₂(CO)₈ (0.1 equiv), N,N,N’-tetramethylthiourea (0.6 equiv) and a solution of the enyne compound (1 equiv) were successively added in dry toluene (20 mL/mmol). Then, the reaction mixture was kept under a CO atmosphere and stirred at 70 °C until disappearance of the starting material as monitored by TLC. Then, the mixture was filtered on Celite and concentrated under reduced pressure. The crude product was purified by flash chromatography using the indicated solvent mixture as eluent.

Molecular modelling. Calculations were performed using SPARTAN Version 5.11. Conformational searches of 36 were carried out using Monte Carlo method within MMFF94 force field, and the AM1 semiempirical method [72] was used to optimize the global minimum conformer. The geometry of the most abundant minimum energy conformer was successively subjected to ab initio single point energy calculation at the 3-21G* (6-31G*) level of quantum chemical theory.

PCA analysis. The web-based public tool ChemGPS-NP was used for PCA analysis of compounds 3–39, to compare their chemical properties with those of blockbuster drugs. ChemGPS-NP can be applied for comprehensive chemical space navigation and exploration in terms of global mapping on to a consistent 8-dimensional map of structural characteristics. The first four dimensions of the ChemGPS-NP map capture 77% of data variance. Chemical compounds were positioned onto this map using interpolation in terms of PCA score prediction. SMILES codes for all compounds were retrieved using ChemBioDraw Ultra 12.0 and submitted to ChemGPS-NP for achieving the corresponding PC scores (see Supporting Information). The PCA data were then used for the construction of PC1 vs PC2.
PMI analysis. Principal moments of inertia analysis was carried out by calculation of the lowest energy conformation of compounds 3–39 and block buster drugs. The conformation calculation was performed using the built-in AMMP molecular mechanics algorithm with default parameters of the VEGA ZZ molecular modelling software package v.3.0.1. Once the lowest energy conformer was calculated, the three principal moments of inertia (Ixx, Iyy, Izz) and normalized principal moments of inertia, npr1 (Ixx/Izz) and npr2 (Iyy/Izz) were determined and plotted on a triangular graph with the vertices (0,1), (0.5,0.5) and (1,1) representing a perfect rod, disc and sphere, respectively.

Supporting Information

Supporting Information File 1
Table of reaction conditions for KA2; experimental procedures, characterization data and copies of 1H and 13C NMR spectra for all new compounds; copies of NOESY-1D, gCOSY, NOESY and cartesian coordinates of compound 36; Smiles codes, PCA and PMI data for compounds 39–3.

References


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Copper-catalyzed enantioselective conjugate addition of organometallic reagents to challenging Michael acceptors

Delphine Pichon, Jennifer Morvan, Christophe Crévisy and Marc Mauduit*

Abstract
The copper-catalyzed enantioselective conjugate addition (ECA) of organometallic nucleophiles to electron-deficient alkenes (Michael acceptors) represents an efficient and attractive methodology for providing a wide range of relevant chiral molecules. In order to increase the attractiveness of this useful catalytic transformation, some Michael acceptors bearing challenging electron-deficient functions (i.e., aldehydes, thioesters, acylimidazoles, N-acyloxazolidinones, N-acylpyrrolidinones, amides, N-acylpyrroles) were recently investigated. Remarkably, only a few chiral copper-based catalytic systems have successfully achieved the conjugate addition of different organometallic reagents to these challenging Michael acceptors, with excellent regio- and enantioselectivity. Furthermore, thanks to their easy derivatization, the resulting chiral conjugated products could be converted into various natural products. The aim of this tutorial review is to summarize recent advances accomplished in this stimulating field.

Introduction
Generating high molecular complexity and controlling multiple stereogenic centers in a minimum number of steps is nowadays one of the most important challenges in organic chemistry for the synthesis of complex chiral molecules. The transition metal (TM)-catalyzed enantioselective conjugate addition (ECA) of nucleophiles to electron-deficient alkenes (Michael acceptors) is one of the most relevant and versatile methods to achieve this goal [1-4]. Among the plethora of metals studied, copper-based catalytic systems proved to be highly efficient for the conjugate addition of various organometallic reagents, such as diorganozinc, triorganoaluminium, and Grignard reagents to Michael acceptors. In that respect, since the pioneering example reported by Alexakis and co-workers in 1993 [5], a wide range of cyclic and acyclic electron-deficient alkenes, such as α,β-unsaturated ketones, esters, nitriles, sulfones, or nitroolefines, was intensively studied, leading to the expected 1,4-products in excellent yields and remarkable enantioselectivities. More recently, tremendous breakthroughs were achieved in this
Enantioselective conjugate addition to challenging Michael acceptors
Copper-catalyzed ECA to α,β-unsaturated aldehydes

Nowadays, β-substituted enals represent probably the most challenging Michael acceptors in the copper-catalyzed ECA of organometallic reagents [11-13]. This challenge is reinforced by the fact that the resulting chiral β-functionalized aldehydes are considered as an important motif that is ubiquitous in numerous natural molecules. However, as depicted in Scheme 1, due to their stronger reactivity than that of usual esters or ketones, a competitive 1,2-addition to the carbonyl function of enals could occur, leading to the corresponding alcohol as a byproduct. Moreover, even if the 1,4-addition is favored, thanks to the copper/ligand catalytic species, the resulting metallic enolate intermediate can also react with the starting material to form the aldol byproduct, significantly altering the yield of the expected 1,4-product (Scheme 1).

The first successful copper-catalyzed ECA to α,β-unsaturated aldehydes with organozinc and Grignard reagents was reported by Alexakis and co-workers in 2010 [14]. After screening various chiral phosphine-based ligands, the combinations of either phosphoramidite L1 with Cu(OTf)2, or (R)-BINAP (L2) with copper thiophenecarboxylate (CuTC) appeared to be the most efficient for the addition of Et2Zn to a variety of cyclic and acyclic aldehydes 1. High 1,4-regioselectivities and promising stereoselectivities ranging from 27 to 90% ee were achieved (Scheme 2a). It is noteworthy that the addition of dimethylzinc was also successfully achieved, as the desired 1,4-methylated
Scheme 2: Cu-catalyzed ECA of α,β-unsaturated aldehydes with phosphoramidite- (a) and phosphine-based ligands (b).
products were exclusively formed in moderate to good yields, with ee values of up to 76%. When the conjugate addition was performed with Grignard reagents, significant amounts of 1,2-products and enols were formed, despite the use of cryogenic conditions. \((R\text{-})\text{BINAP (L2)}\) gave the best regio- and enantioselectivity, with 62% of the 1,4-product and 89% ee with EtMgBr (Scheme 2b). To overcome the low regioselectivity, the authors took into account previous works showing that the 1,4-regioselectivity in the addition of cuprates to enals could be improved in the presence of a slight excess of TMSCl [15-19]. Indeed, using TMSCl in combination with \((R\text{-})\text{ TolBINAP (L3)}\), a promising 85% regioselectivity was observed, without altering the enantioselectivity (90% ee), whereas only 32% of the desired 1,4-product was obtained without TMSCl [20]. With those optimized conditions, various enals and Grignard reagents were screened. Nevertheless, despite the presence of TMSCl, the 1,4:1,2 ratio varied significantly (from 85:15 to 10:90), while the level of enantioselectivity remained relatively good, reaching up to 90%.

Following this, Alexakis and Quintard invented an efficient stepwise one-pot copper-catalyzed asymmetric ECA/organocatalyzed α-substitution of enals [21]. By using \((R\text{-})\text{BINAP (L2)/CuTC}\) in combination with chiral prolinol derivatives L4–6 as organocatalysts, various α,β-functionalized aldehydes were synthesized in good isolated yields (57–74%) and remarkable enantioselectivity (99%) from diethylzinc or dimethylzinc as nucleophiles and vinyl sulfones as electrophiles (Scheme 3). Of note,
Scheme 4: Combination of copper and amino catalysis for enantioselective β-functionalizations of enals.

The last report on ECAs of enals [23] was disclosed in 2016 by Alexakis and co-workers [24]. They achieved to develop three sets of optimized conditions for the CuTC-catalyzed conjugate addition of diorganozinc compounds, Grignard, and triorganoaluminium reagents to α,β-unsaturated aldehydes (Scheme 5). With diethyl- and dimethylzinc, and in the presence of the most efficient chiral ligand (R)-H8-BINAP (L7), moderate to excellent regioselectivities (1,4:1,2 ratios up to 100:0) were observed, and the desired 1,4-products were formed with remarkable enantioselectivities (58 to 96% ee). With Grignard reagents, the best ee values (45 to 90%) were obtained with (R)-TolBINAP (L3), but despite the presence of TMSCl, the regioselectivities remained modest, with a highest 1,4:1,2 ratio of 85:15. At last, (R)-SEPHOS (L8) promoted the conjugate addition of Me3Al to cinnamaldehyde, with a remarkable 96% ee and a moderate 1,4:1,2 ratio. However, albeit no trace of aldol byproduct was detected, the reaction was incomplete (66% conversion). The use of TMSCl improved the conversion to 88%, but this was detrimental to the enantiocontrol (8% ee). These methodologies were applied to the straightforward synthesis of valuable (R)-citronellal and (S)-Floryhydral®[8], which were obtained with excellent enantioselectivities (87 and 96%, respectively).

Similarly, a cocatalyzed enantioselective β-functionalization of enals was developed by Córdova, Ibrahem, and co-workers in 2011 (Scheme 4) [22]. By mixing high catalytic loadings of Cu(OTf)2, PPh3, and TMS-protected diarylprolinol L4, the conjugate addition of Et2Zn or Me2Zn to various β-substituted enals proved to be highly enantioselective (ee up to 96%), but moderate to good 1,4:1,2 ratios were obtained (51:49 to 97:3).

Of note, chiral phosphines were also screened, but without any improvement of selectivity. Furthermore, this methodology was then efficiently applied to the total synthesis of several bisabolane sesquiterpenes, which exhibited anticancer and antimicrobial activities or are employed as ingredients in perfumes and cosmetics (Scheme 4).
As highlighted by these pioneering works, the direct copper-catalyzed conjugate addition of organometallic reagents to α,β-unsaturated aldehydes still remains an important challenge. Albeit some promising excellent regioselectivities and high enantioselectivities were achieved, this was often limited to a few organometallic reagents/enal substrates, as mentioned above. In that respect, indirect pathways were developed as alternative strategies, involving electron-deficient functions that can subsequently easily be converted to aldehydes.

**α,β-Unsaturated thioesters**

In 2005, Feringa, Minnaard, and co-workers were the first to report the ECA of Grignard reagents to α,β-unsaturated thioesters [25]. Advantageously, the latter were also readily accessible but significantly more reactive than α,β-unsaturated esters. Indeed, the thioester fragments featured a reduced electron delocalization compared to oxoesters, which resulted in a higher reactivity in conjugate additions, even with the less reactive MeMgBr. As depicted in Scheme 6, excellent yields and remarkable enantioselectivities (up to 96%) were obtained in ECAs of linear aliphatic Grignard reagents (in particular MeMgBr) to a wide range of substrates, catalyzed by CuBr·SMes₂/(R,S)-Josiphos ([L9]).

However, the catalytic system was poorly selective toward sterically hindered organomagnesium nucleophiles (15–25% ee). The synthetic versatility of the thioester function was illustrated in the synthesis of (−)-lardolure (26% overall yield over 12 steps) via a relevant diastereoselective and enantioselective iterative route, affording the highly desirable deoxypropionate moiety in high 97% de. The Josiphos ([L9])/CuBr·SMes₂ catalytic system was also efficient to promote the ECAs of MeMgBr to the less reactive aromatic α,β-unsaturated thioesters (ee...
values up to >99%) [26]. In order to extend their methodology to less reactive bulky Grignard reagents and/or substrates, a catalytic system of wider application, involving (S)-TolBINAP (ent-L3)/CuI was developed by the same authors [26]. The expected 1,4-products were isolated in good yields and moderate to excellent enantioselectivities (up to 99% ee, Scheme 7), depending on the steric hindrance of the reagent. Unfortunately, the addition of PhMgBr remained unsuccessful. This powerful catalytic protocol was illustrated by Bates and Sridhar in the enantioselective total synthesis of (−)-mintlactone [27]. The key step, furnishing the β-methylated thioester 8j, was accomplished in a good yield of 84% and a high ee of 94% (Scheme 7).

In 2008, Feringa and Minnaard evaluated the ECA of Grignard reagents to γ-substituted α,β-unsaturated thioesters that could lead to vicinal (i.e., 1,2-relation) dialkyl arrays, a highly desirable moiety that is ubiquitous in a wide range of natural products [28]. As depicted in Scheme 8, TolBINAP (L3)/CuI, which appeared to be a better catalytic system than Josiphos (L9)/CuBr-SMe₂, afforded either the syn or anti 1,4 product 13 in good isolated yields and excellent diastereoselectivities and enantioselectivities (dr up to 99:1 and ee up to >99.5). The value of the protocol was successfully illustrated through the enantioselective total synthesis of (−)-lasiol and (+)-faranal, two useful natural pheromones.

Shortly after, Feringa, Minnaard, and co-workers demonstrated the efficiency of (S,R)-reversed Josiphos (L10) in the copper-catalyzed 1,6-ECA of MeMgBr to α,β,γ,δ-bisunsaturated thioesters [29,30]. The expected 1,6-products were selectively formed (the 1,6:1,4 ratio ranged from 85:15 to 99:1) in high yields (78–88%) and good enantioselectivities (82–89%, Scheme 9). It is worth to note that this protocol failed in the case of linear dienoates [29]. Interestingly, after a subsequent reconjugation step in the presence of DBU, the resulting enantioenriched γ-methylated α,β-unsaturated thioester 18a was subsequently reacted in a 1,4-ECA reaction catalyzed by Josiphos (L9)/CuBr-SMe₂. Using both enantiomers of the chiral ligand, either anti- or syn-1,3-deoxypropionate units were pro-
Scheme 7: Improved Cu ECA of Grignard reagents to α,β-unsaturated thioesters, and their application in the asymmetric total synthesis of (-)-mint-lactone.

Scheme 8: Catalytic enantioselective synthesis of vicinal dialkyl arrays via Cu ECA of Grignard reagents to γ-substituted α,β-unsaturated thioesters.
scheme 9: 1,6-cu eca of memgbr to α,β,γ,δ-bisunsaturated thioesters: an iterative approach to deoxypropionate units.

duced in good yields and excellent enantioselectivities (85–92% ee). Furthermore, an iterative procedure was also performed leading to all-syn or anti/syn-5,7,9-stereotriads, with high yields and stereoselectivity. This methodology was also tested on linear polyenic thioesters [9]. The challenging 1,8- and 1,10-products 21a/b were obtained, but the stereoselectivity dropped when the distance between the reacting olefin and the ester function was increased (1,8-eca 72% ee; 1,10-eca 45% ee). However, the regioselectivity (59–86%) and yield (44–63%) remained decent.

The efficiency of tolbinap (l3)/cuI was also demonstrated in the ECA of Grignard reagents to the 4-chloro-α,β-unsaturated thioester 22 [31]. Interestingly, the presence of the internal chloro leaving group allowed a powerful tandem conjugate addition–enolate trapping that led to valuable trans-1-alkyl-2-substituted cyclopropanes (Scheme 10). Various Grignard reagents were used, affording the corresponding cyclopropanes in moderate to high yields (50–92%) and good to excellent ee values (70–96%), except for PhMgBr (26% ee).

In 2010, Hall and Lee described a successful synthesis of enantioenriched boronate derivatives through catalytic ECA of Grignard reagents to 3-boronyl α,β-unsaturated thioesters (Scheme 11) [32]. By applying an L3/Cu catalytic protocol previously developed by Feringa and Minnaard, MeMgBr and a range of aromatic Grignard reagents were selectively introduced, leading to the expected 1,4-products in high yields.
Scheme 10: Tandem Cu ECA/intramolecular enolate trapping involving 4-chloro-α,β-unsaturated thioester 22.

Scheme 11: Cu ECA of Grignard reagents to 3-boronyl α,β-unsaturated thioesters.

(50–82%) and ee values (82–98%). Unfortunately, ortho-substituted aromatic or hindered alkenyl reagents led to the corresponding products without showing any enantioselectivity.

Very recently, Fletcher and Gao reported the first copper-catalyzed ECA of alkylzirconium reagents to α,β-unsaturated thioesters [33]. Starting from diversely functionalized alkenes, the resulting hydrozirconated adducts were reacted with various β-substituted Michael acceptors in the presence of CuCl and the chiral phosphoramidite L11 (Scheme 12). Remarkably, the corresponding 1,4-products were isolated in moderate to good yields (around 70%) and up to 99% ee. The high versatility of the protocol was illustrated by the synthesis of commercially relevant fragrances (phenoxanol and hydroxycitronellal). Additionally, an efficient iterative route was also described, allowing to produce the highly functionalized deoxypropionate fragment 30 in good overall yields and excellent stereocontrol for all stereogenic centers (up to 98:2 dr).
The pioneering and successful use of α,β-unsaturated acylimidazoles as Michael acceptors in enantioselective catalysis was reported by Evans and co-workers in 2005 [34]. The selected asymmetric transformation was the Friedel–Crafts 1,4-addition involving indole derivatives as nucleophiles, catalyzed by a scandium(III) triflate complex with chiral bis(oxazolinyl)pyridine ligands. As highlighted by Evans, the acylimidazole moiety constituted a privileged surrogate of esters, amides, ketones, and aldehydes. Indeed, this peculiar function, which was readily accessible from the corresponding aldehydes or Weinreb amides, could be efficiently converted into a wide range of carbonyl derivatives, as depicted in Scheme 13.

The successful use of α,β-unsaturated acylimidazole in Cu ECAs using organometallic reagents has been introduced very recently. Pioneering works in this field were published in 2011 by Roelfes, Liskamp, and co-workers, with the 1,4-addition of dimethyl malonate to cinnamyl 2-acyl-1-methylimidazole (31). Unfortunately, in the presence of Cu(NO₃)₂ and the triazacyclo-
Scheme 13: Conversion of acylimidazoles into aldehydes, ketones, acids, esters, amides, and amines.

In 2012, Sawamura and co-workers described the first highly enantioselective copper-catalyzed conjugate addition of alkyl boranes to $\alpha,\beta$-unsaturated 2-acyl-1-methylbenzimidazoles \textit{33} [36]. Based on a previous study dealing with the CuCl/IMes-catalyzed addition of various alkylated 9BBN derivatives [37], the authors screened a set of various chiral NHC precursors. The imidazolium compound \textit{L13} appeared to be the most efficient one, affording the desired 1,4 products in high yields (57 to 93\%) and excellent ee values (up to 93\%, Scheme 15). Advantageously, this methodology was highly tolerant towards a wide range of functional groups, whether on alkylboranes or on substrates.

Scheme 14: Cu ECA of dimethyl malonate to $\alpha,\beta$-unsaturated acylimidazole \textit{31} with triazacyclophane-based ligand \textit{L12}. 
In 2015, Mauduit, Campagne, and co-workers set up a highly enantioselective 1,4-addition of dimethylzinc to a wide scope of α,β-unsaturated acylimidazoles 35 [38]. Among the various ligands screened in combination with copper(II) triflate, the hydroxyalkyl-chelating NHC precursor L14 proved to be the most efficient one, giving the 1,4 product with moderate to good yields (34–86%) and excellent enantioinduction (86 to 95% ee, Scheme 16). The methodology was successfully applied to various extended Michael acceptor systems (dienic or trienic acylimidazoles), leading preferably to the corresponding 1,4 products in moderate to good yields (28–85%) with remarkable regio- (>95%) and enantioselectivities (91–95% ee) [39]. Interestingly, DFT calculations supported the crucial role of the imidazole moiety towards the 1,4-addition (vs 1,6 or 1,8) [39]. Thanks to the efficient post-transformation of the acylimidazole function, the synthetic potential of this methodology was illustrated in the synthesis of relevant molecules, such as a ionone derivative, (+)-ar-turmerone, and (+)-Florhydral®, which were formed in good yields, without alteration of their optical purity [38,39].

Moreover, an iterative Cu ECA process allowing the selective introduction of a second methyl stereogenic center was then explored to develop a straightforward access to 1,3-deoxypropionate units, a scaffold ubiquitous in numerous natural products (Scheme 17) [40]. Starting from enantioenriched β-methylated aldehyde 37, the regeneration of the α,β-unsaturated 2-acyl-1-methylimidazole moiety was performed in high yield and E/Z selectivity via a two-step protocol. The resulting Michael acceptor was then engaged in an ECA to afford the expected 1,3-dimethyl product in 69% yield and a good diastereomeric excess of 94% (Scheme 17). Following this iterative methodology, the synthesis of 3,5,7-all-syn- and anti,anti-stereotriads 40a/b were successfully achieved in high diastereomeric ratios (up to >95:5) and good overall yields from (+)-citronellal.

More recently, Mauduit, Campagne, and co-workers reported an efficient Cu/Taniaphos-catalyzed β-borylation of an α,β-unsaturated acylimidazole, leading to various enantioenriched β-hydroxy products after oxidation (up to >98% ee) [41]. Interestingly, following the aforementioned iterative ECA strategy, the postfunctionalized chiral acylimidazole 41 derived from (S)-citronellal was efficiently converted to highly desirable anti,syn- and anti,anti-3,5,7-(Me,OR,Me)-substituted products 42a/b, which were isolated in good yields and excellent diastereomeric ratios (up to >95:5, Scheme 18).

Scheme 15: Cu/L13-catalyzed ECA of alkylboranes to α,β-unsaturated acylimidazoles.
**α,β-Unsaturated N-acyloxazolidinone, N-acylpyrrolidinone, and amide derivatives**

Similar to acylimidazole Michael acceptors, the first use of α,β-unsaturated N-acyloxazolidinones was also described in asymmetric Friedel–Crafts 1,4-additions catalyzed by chiral copper/bisoxazolidine Lewis acids [42-46]. Thanks to the easy post-transformation of the oxazolidine moiety, the resulting enantio-enriched products (up to 99% ee) were successfully converted to relevant molecules, such as trans-whisky lactone [43].

In 2003, Hoveyda and Hird reported the first 1,4-addition of alkylmetal nucleophiles to α,β-unsaturated N-acyloxazolidinones (Scheme 19) [47]. The chiral triamidophosphane ligand L15a as a copper(I) triflate complex efficiently promoted the catalytic conjugate addition of dialkylzinc species to various N-acyloxazolidinone Michael acceptors, in most of the cases with high isolated yields (61 to 95%) and excellent enantio-selectivities (up to >98%). Furthermore, the resulting enantio-enriched β-alkylated N-acyloxazolidinones could be converted to various derivatives (aldehydes, ketones, Weinreb amides, or carboxylic acids) in good yields and without alteration of the ee values. In 2006, aminohydroxyphosphine L15b was used as a new designer ligand by Nakamura and co-workers for the addition of diethylzinc to crotonyl N-acyloxazolidinone [48]. The 1,4-product was also formed in high enantioselectivity (>98% ee) and high yield (91%).

---

**Scheme 16:** Cu/hydroxyalkyl-NHC-catalyzed ECA of dimethylzinc to α,β-unsaturated acylimidazoles.
The same year, Pineschi et al. evaluated various $\alpha,\beta$-unsaturated acyl derivatives for the copper/($R,S,S$)-phosphoramidite L16-catalyzed addition of diethylzinc (Scheme 20) [49]. Although the Michael acceptor bearing the N-acyloxazolidinone moiety that was successfully used by Hoveyda (95% ee) gave a lower enantioselectivity (64%), a more satisfactory enantiocontrol was obtained with the substrate having a 2-pyrrolidinone fragment (87% ee). The scope was then extended to various $\alpha,\beta$-unsaturated N-acyl-2-pyrrolidinones and dialkylzinc reagents, leading to the corresponding 1,4-products in low to good yields (7–88%), with good to excellent enantiom­duction (60 to >99% ee). Trimethylaluminium reagents were also investigated, but unfortunately, only low ee values were observed (20–36% ee), whereas no reactivity was observed with $\alpha,\beta$-unsaturated amides.

Although Pineschi’s conditions were ineffective for amides [49], Harutyunyan and co-workers achieved an important breakthrough by reporting the first enantioselective alkylation of $\alpha,\beta$-unsaturated amides [50]. Indeed, due to their poor reactivity compared to other Michael acceptors, catalytic asymmetric conjugate additions of organometallic reagents to $N,N$-
Scheme 19: Cu-catalyzed ECA of dialkylzinc reagents to α,β-unsaturated N-acyloxazolidinones.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Yield</th>
<th>Ee</th>
</tr>
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<tbody>
<tr>
<td>44a</td>
<td>95%</td>
<td>95% ee</td>
</tr>
<tr>
<td>44b</td>
<td>61%</td>
<td>93% ee</td>
</tr>
<tr>
<td>44c</td>
<td>95%</td>
<td>&gt;98% ee</td>
</tr>
<tr>
<td>44d</td>
<td>91%</td>
<td>86% ee</td>
</tr>
</tbody>
</table>

L15a (2.4–6 mol %), (CuOTf)$_2$:C$_6$H$_6$ (0.5–2.5 mol %), toluene, −15 °C to 0 °C, 8 examples, 61–95% yield, 76 to >98% ee

L15b (6 mol %), Cu(OTf)$_2$ (5 mol %), CH$_2$Cl$_2$, 0 °C

>98% yield, 95% ee from 44a

74% yield, 93% ee from 44b

81% yield, 93% ee from 44b

Scheme 20: Cu/phosphoramidite L16-catalyzed ECA of dialkylzincs to α,β-unsaturated N-acyl-2-pyrrolidinones.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Yield</th>
<th>Ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>49a</td>
<td>75%</td>
<td>95% ee</td>
</tr>
<tr>
<td>49b</td>
<td>75%</td>
<td>81% ee</td>
</tr>
<tr>
<td>49c</td>
<td>84%</td>
<td>&gt;99% ee</td>
</tr>
<tr>
<td>49d</td>
<td>74%</td>
<td>94% ee</td>
</tr>
</tbody>
</table>

R = alkyl, aryl, aikenes

toluene, −78 °C to 0 °C, 23 examples, 7–88% yield, 60 to >99% ee

(RS,S)-L16
dialkylenamides remained a real challenge. However, thanks to the synergistic action of the boron-based Lewis acid BF₃∙Et₂O, CuBr·SMe₂, and the chiral (R,S)-Josiphos ligand (L₉), an efficient (yields up to 86%) and highly regio- and enantioselective (ee values up to 99%) protocol was developed for 1,4-additions of various Grignard reagents to a wide scope of substrates (Scheme 21). Notably, the introduction of methyl and functionalized alkyl groups was performed with remarkable stereoselectivity (97–99%). Furthermore, this catalytic system was easily upscalable (up to 10 g), and the chiral catalyst could be recycled without any loss of efficiency. Unfortunately, although a wide range of Grignard reagents led to excellent results, PhMgBr provided low conversion and the racemic 1,4-product. Additionally, amide substrates featuring a bis(para-methoxybenzyl) moiety could be converted into relevant β-alkyl-substituted chiral amines, ubiquitous in numerous pharmaceutical ingredients, such as 52, a direct precursor of a drug candidate. Moreover, tandem ECA/enolate trapping was also studied, providing the trans-cyclopentane product 56 as a single diastereoisomer (92% ee).

In 2018, the same authors reported the 1,6- and 1,4-additions of various Grignard reagents to a wide scope of conjugated dienyl amides (Scheme 22) [51]. Interestingly, the authors observed...
that the regioselectivity was directed by the substituent in the δ-position of the substrate: dienic amides featuring linear or functionalized aliphatic substituents in the δ-position led predominantly to 1,6-products, whereas those featuring electron-rich and electron-poor aromatic, heteroaromatic, and branched aliphatic substituents in the δ-position afforded preferably the 1,4-products. Importantly, when the morpholine moiety was used as N-substituent, the addition of diethylzinc to the enamide afforded the 1,6-addition product with 78% isolated yield and 91% ee. It is worth to underline that the morpholine group could easily allow further postfunctionalizations. Furthermore, thanks to the highly 1,6-enantioselective additions of trimethylaluminum to three α,β-unsaturated N-acylpyrroles with moderate to good yields (54 to 87%) and excellent enantioselectivities (94 to 97% ee, Scheme 23) [52], this methodology was successfully applied to the synthesis of various natural molecules, such as (S)-Florhydral® and (S)-(+)ar-turmerone or key intermediates in the synthesis of 8-deoxyanisatin and frondosin.

**Conclusion**

The enantioselective Cu-catalyzed conjugate addition of organometallic reagents to Michael acceptors has been exten-
Scheme 23: Cu-catalyzed ECA of trimethylaluminium to N-acylpyrrole derivatives.

sively studied for many decades and led to remarkable results. However, for a long time, some classes of Michael acceptors (α,β-unsaturated aldehydes, thioesters, acylimidazoles, N-acyloxazolidinone, N-acylpyrrolidinone, amides, N-acylpyrroles) have been neglected to varying degrees, probably owing to their particular reactivity, which led to less impressive results. Nevertheless, these substrates present a high potential in total synthesis, since the chiral products can be easily transformed into various natural compounds. For example, the aldehyde function, which is directly obtained from α,β-unsaturated aldehydes or is accessible through postderivatization of either acylimidazole or thioester functions, is present in many natural compounds and is also a key functional group for many synthetic strategies. Furthermore, some of the functional groups listed above can be converted into various other synthetically useful groups, such as ketones, esters, carboxylic acids, and (Weinreb) amide groups.

More recently, some works were reported, which showed that through a judicious selection of chiral ligands and a fine-tuning of the reactivities of both partners, interesting selectivities could be reached with these more challenging electron-deficient alkenes, including, in some cases, di- or trienic acceptors, which accordingly extends the scope and the synthetic applicability of the method. The potential of the methodology has been illustrated through the efficient conversion of some 1,4-products into various chiral natural products. In addition, iterative procedures leading to chiral 1,3,5-(Me,Me,Me) and 1,3,5-(Me,OH,Me) motifs in a stereocontrolled way were successfully applied from α,β-unsaturated acylimidazoles and α,β-unsaturated thioesters, and thus opening a new field for the total synthesis of natural products. We hope that the results collected in this review will encourage chemists on one hand to continue the search for improved procedures combining simple, easily accessible chiral ligands, lower catalytic loadings, high ee values and productivity, and a wide scope, and on the other hand, to include this highly promising methodology in many synthetic strategies.

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References


See for a review on iterative ECA processes.

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