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Recent updates on the asymmetric synthesis of 3-fluoro-3-substituted oxindole from 3-fluorooxindoles

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Abstract

Organofluorine compounds vastly found in numerous biologically active molecules in the areas of materials science, agricultural chemistry, and pharmaceutical chemistry due to the special nature of fluorine to enhance molecular characteristics, such as pKa, lipophilicity, metabolic stability, or even permeability. Stereoselective strategies for synthesis of chiral fluoro-organic compounds are a dynamic research area, as such entities are proficient of exhibiting entirely distinct modes of, and/or improved, activities. On the other hand, chiral oxindole scaffolds, particularly chiral 3,3'-disubstituted oxindoles bearing a β-aminocarbonyl unit, is of special significance for their structurally determining existence in diverse natural products, biologically and pharmaceutically connected molecules. Knowing the significance of both fluorinated organic molecules and chiral 3,3'-disubstituted oxindole moieties, asymmetric synthesis of 3-fluoro-3-substituted oxindoles has put much attention and various recent publications were reported. In this paper a critical review on the recent synthesis of 3-fluoro-3-substituted oxindole compounds starting from 3-fluorooxindole will be summarized.

Keywords: Asymmetric synthesis, 3-fluorooxindole, catalysis, chiral 3,3'-disubstituted oxindole

1. Introduction

The specific nature of fluorine like high NMR sensitivity, properties to improve binding affinity, metabolic stability and bioavailability when present in organic molecules, makes it exceedingly significant substrates in medicinal chemistry (Fig. 1) [1-3].

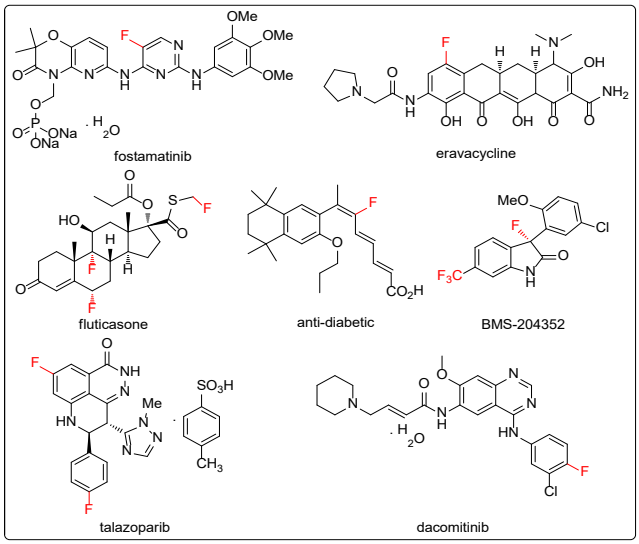

Fig 1. Fluorinated bioactive compounds drugs and oxindole unit.

The results were observed for 20-50 % of pharmaceuticals on the retail, agrichemicals bearing at least one fluorine atom [4-8]. Radiotracers labeled with 18F nuclei were used for medicinal applications through positron emission tomography−computed tomography (PET-CT) [9-10]. Currently fluorine based solar cells and functional materials were designed and developed based on the stabilizing and electronic impacts of fluorination on material characteristics [11-13].

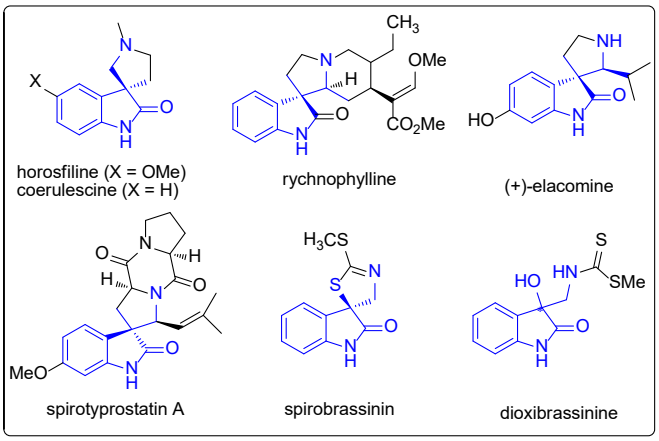

Fig 2. Biologically important 3,3'-disubstituted-2-oxindole motifs.

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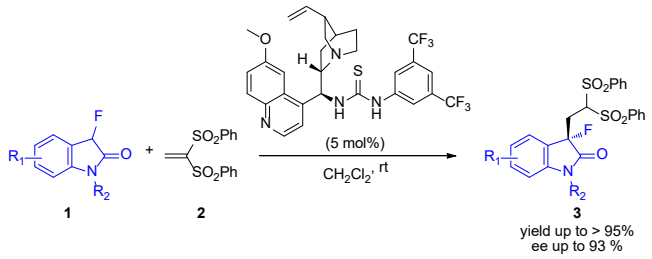
3,3'-disubstituted 2-oxindole structural units are critical component of natural products and bioactive molecules, especially chiral oxindole scaffolds are of specific significance for their structurally determining entity in a number of natural product entities, biologically and pharmaceutically relevant molecules (Fig. 2) [14-20].

Molecular complexity induced by the quaternary stereogenic center of 3,3-disubstituted oxindole motifs draws much more consideration to the synthetic community to synthesize the novel biologically and pharmaceutical active natural product-mimicked compound classes. Currently, numerous asymmetric organocatalytic methodologies were established and reported the preparation of quaternary chiral center contained 3,3-disubstituted fluoro-2-oxindole derivatives utilizing 3-fluoro oxindoles as pro-nucleophile [21-28]. All this results will be summarized subsequently.

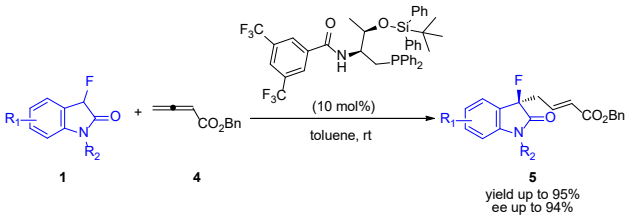
2. Brief Rreview

In 2013, Lu and co-workers first reported the preparation of 3-fluoro-3-substituted oxindole derivatives **3** via Michael additions of 3-fluorooxoindoles **1** to 1,1-bis(phenylsulfonyl)ethene **2** (Scheme 1) asymmetrically in presence of organocatalysts [21]. The reaction proceeded smoothly under room temperature to obtain the desired compounds with perfect yield (up to >95%) and enantioselectivity (up to 93%).



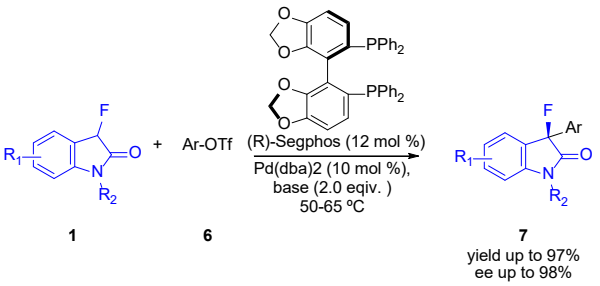
Scheme 1. Asymmetric Michael additions of 3-fluorooxoindoles **1** to 1,1-bis(phenylsulfonyl)ethene **2**.

Next in 2015, the Lu group established asymmetric Michael type γ-addition reaction with 3-fluorooxindoles **1** with 2,3-butadienoates **4** using *L*-threonine derived phosphine-amide catalyst (Scheme 2) [22]. During this reaction, C-F quaternary center bearing 3-fluoro-3-allyloxindoles **5** were obtained with high yields (yield up to 95%) and enantioselectivities (up to 94% ee).



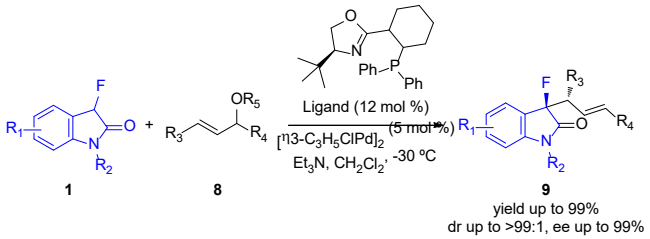
Scheme 2. Asymmetric Michael type addition reaction with 3-fluorooxindoles **1** with 2,3-butadienoates **4**.

In 2017 John F. Hartwig and co-workers established the asymmetric Pd-catalyzed arylation of 3-fluorooxindoles **1** with aryl triflates **6** using (*R*)-Segphos as ligand to obtain α-aryl-3-fluorooxindoles **7** with very high yields and enantioselectivities (Scheme 3, yield up to 97%, ee up to 98%) [23].



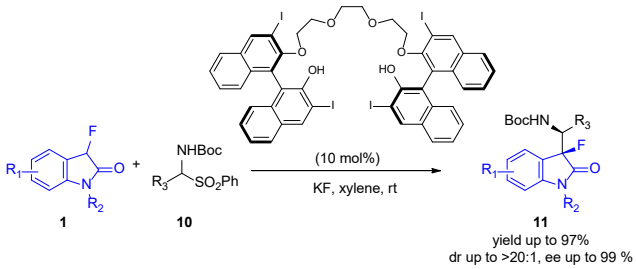
Scheme 3. Asymmetric arylation reaction of 3-fluorooxindoles **1** with aryl triflates **6**.

In the same year, Wolf group reported asymmetric allylic alkylation reaction of 3-fluorooxindoles **1** with allylic acetates/carbonates **8** using Pd-based catalyst and (*S*)-*t*Bu-PHOX ligand (Scheme 4) [24]. The reaction was proceeded smoothly to obtain fluorinated oxindoles **9** containing four contiguous chiral centers high yield (up to 99%), enantioselectivities (up to 99%) and diastereoselectivities (up to >99:1) with excellent regioselectivity (up to 15:1).



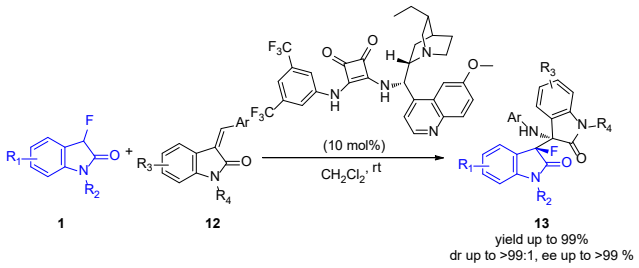
Scheme 4. Asymmetric allylic alkylation reaction of 3-fluorooxindoles **1** with allylic acetates/carbonates **8**.

Subsequently, in 2017, we reported direct organocatalytic Mannich reaction of 3-fluoro-oxindoles **1** with bench-stable precursors of sensitive imines α-amidosulfones **10** using a chiral cation-binding catalyst oligoethylene glycol to synthesize a large number of chiral 3,3-disubstituted oxindole compounds **11** having a β-fluoroamine unit (Scheme 5) [25]. The reaction proceeded very smoothly to obtain the product **11** in good yields (up to 97%) and stereoselectivity (up to 99% ee, dr >20:1 for syn).



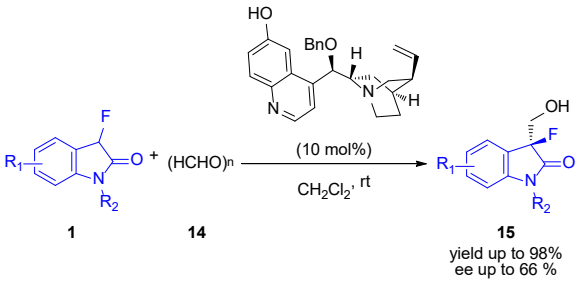
Scheme 5. Asymmetric organocatalytic Mannich reaction of 3-fluoro-oxindoles **1** with α-amidosulfones **10**.

In 2018, Da-Ming Du and co-worker reported the preparation of fluorinated 3,3′-bisoxindoles **13** via asymmetric organocatalytic Mannich reaction of 3-fluorooxindoles **1** to isatin-derived imines **12** using squaramide-catalyst for in perfect yields with diastereo- and enantioselectivities (Scheme 6, up to 99% yield, >99:1 dr and >99% ee) [26].



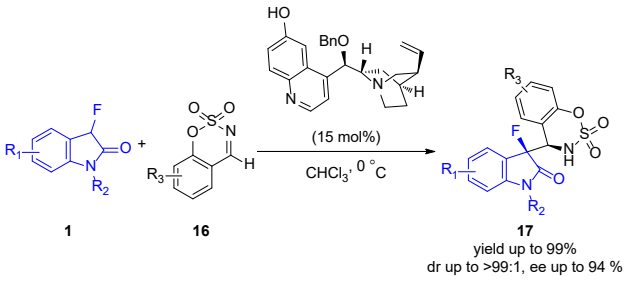
Scheme 6. Asymmetric Mannich reaction of 3-fluoro-oxindoles **1** to isatin-derived imines **12**.

Same year, Ren, Li, and co-workers developed cinchona alkaloid bifunctional catalyst based an organocatalyzed aldol reaction of 3-fluorooxindoles **1** with paraformaldehyde **14** using 10 mol% catalyst loading, to obtain chiral 3-fluoro-3-hydroxymethyl oxindoles **15** in excellent yields (up to 98%) with moderate to good ee values (Scheme 7, ee up to 66%) [27].



Scheme 7. Asymmetric aldol reaction of 3-fluorooxindoles **1** with paraformaldehyde **14**.

Quite recently, Ya Li and co-workers reported Mannich-type asymmetric reactions of 3-fluorooxindoles **1** and cyclic benzo-fused *N*-sulfamidate aldimines **16** using cinchona alkaloid catalyst to obtain the preferred products **17** in yield up to 99% with an high enantiomeric excess (up to 94%, Scheme 8) [28].



Scheme 8. Asymmetric organocatalytic Mannich reactions of 3-fluorooxindoles **1** with cyclic imines **16**.

3. Conclusion

In summary, all the publications related to the asymmetric metal/organocatalyzed reactions of 3-fluorooxindoles as a pro-nucleophile were systematically reviewed. Further design of the catalytic reactions using 3-fluorooxindoles pro-nucleophile for the synthesis of other library of molecules can be initiated with the references herein.

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