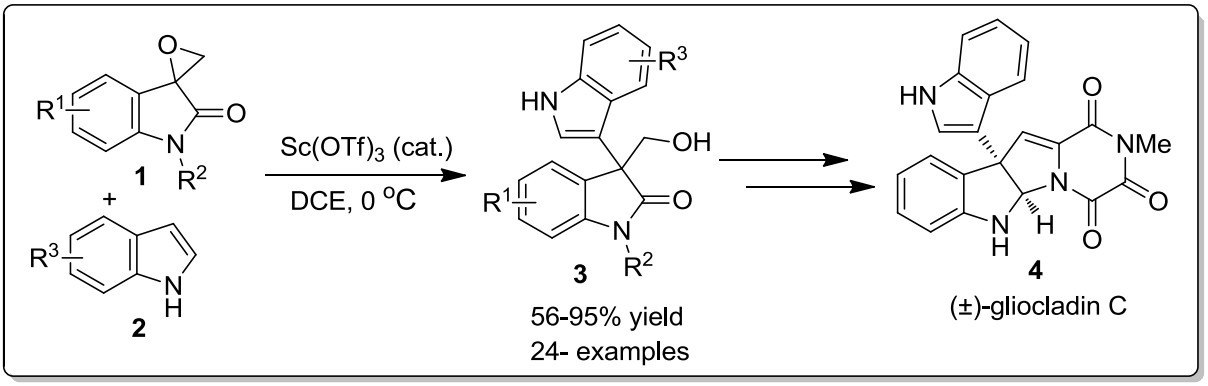
Exploring the Reactivity of Spiro-epoxyoxindoles at Spiro-center towards the Synthesis of C3-Aryl/Heteroaryl Indole Alkaloids

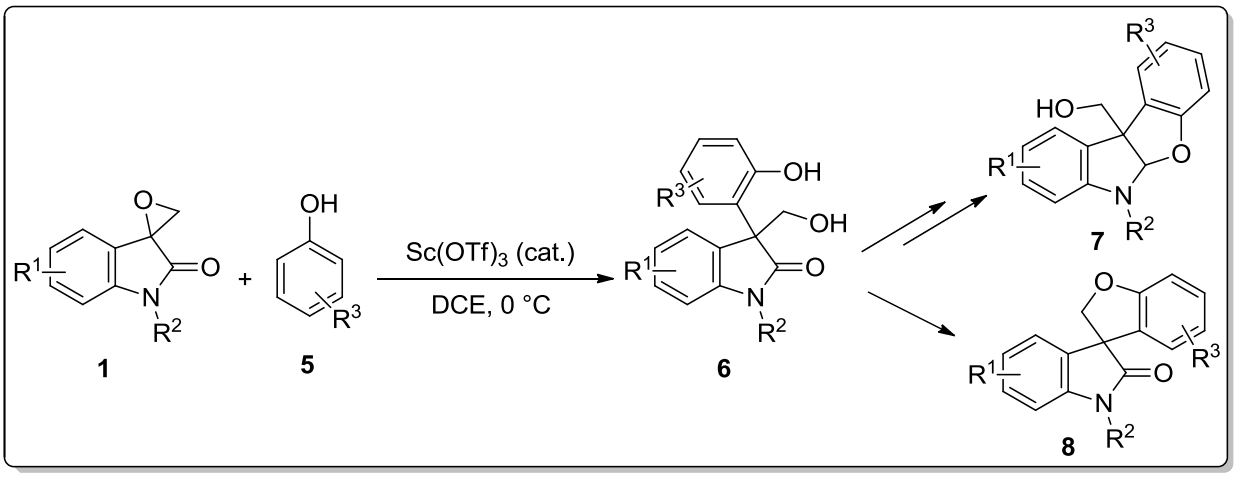
Indole alkaloids possess a significant space in the annals of organic chemistry. Among the large indole kingdom, specifically, polymeric indole alkaloids have attracted a significant amount of attention from the synthetic community in recent decades. The progress of this field continues unabated. Due to their diverse molecular architecture and a broad spectrum of biological as well as pharmacological activities, these compounds have received the utmost attention.

A highly efficient, atom economic and divergent protocol for the gram scale synthesis of 3-(3-indoyl)-oxindole-3-methanols were developed via Lewis Acid-catalyzed, regioselective ring opening of spiro-epoxyoxindoles with indoles. This method produced a large library of 3-(3-indoyl)-oxindole-3-methanols by a combination of different spiro-epoxyoxindole and indoles. The Friedel-Crafts adduct 3-(3-indoyl)-oxindole-3-methanols is efficiently utilized for the formal total synthesis of epipolythiodiketopiperazine alkaloids such as (±)-Gliocladin C. This is the first report for the regioselective ring opening of spiro-epoxyoxindole with carbon nucleophile particularly at the spiro-center.



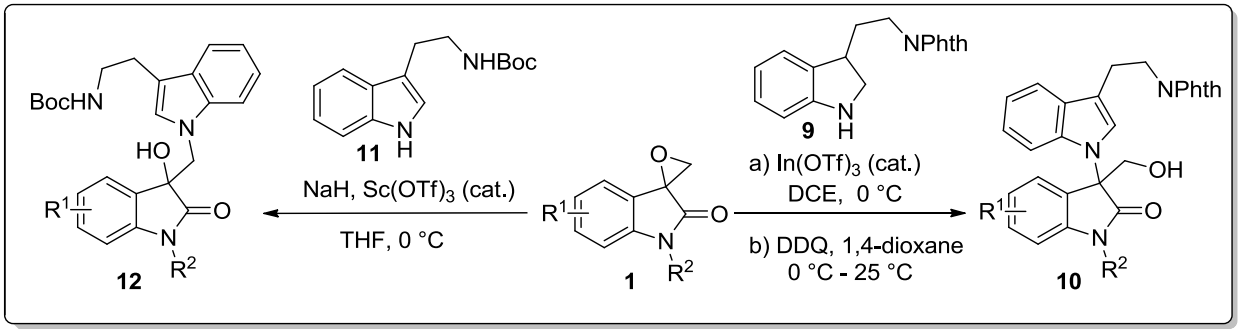
Scheme 1

We have developed a highly efficient Lewis acid catalyzed Friedel-Crafts reaction of phenols and spiro-epoxyoxindoles with excellent regioselectivity at the spiro-center under mild conditions. The Friedel-Crafts adduct 3-(hydroxymethyl)-3-(2-hydroxyaryl)indolin-2-one is efficiently utilized for the synthesis of *N*-methyl analogue of (±) XEN907 and tetracyclic dihydro-benzofuro[2,3-b]indoline having -CH_2OH unit, a key intermediate for the synthesis of diazonamide A and azonazine.



Scheme 2

We have established the direct synthesis of C(3)–N(1′) unsymmetrical bisindole through Lewis acid catalyzed regio- as well as chemoselective coupling of spiro-epoxyoxindoles with tryptamine with good yield. This is the first report for the regioselective ring opening of spiro-epoxyoxindole with nitrogen nucleophile particularly at the spiro-center. We also have developed the synthesis of the new class of bisindoles, C(3)–N(1′) diindolylmethane via base mediated and Lewis Acid-catalyzed coupling of spiro-epoxyoxindole with tryptamine.



Scheme 3

Apart from previously performed Lewis acid catalyzed F-C reactions, we have developed Brønsted acid assisted regioselective ring-opening of a range of spiro-epoxyoxindoles with indoles and arenes in an organic solvent as well as in-water as an alternative.

***Key Words**:* 3-(3-indoyl)-oxindole-3-methanol; *Lewis Acid; spiro-epoxyoxindole; Friedel–Crafts Reaction; 3-(hydroxymethyl)-3-(2-hydroxyaryl)indolin-2-one; benzofuro[2,3-b]indoline; C(3)–N(1') unsymmetrical bisindole; C(3)–N(1') diindolylmethane; Brønsted acid.*