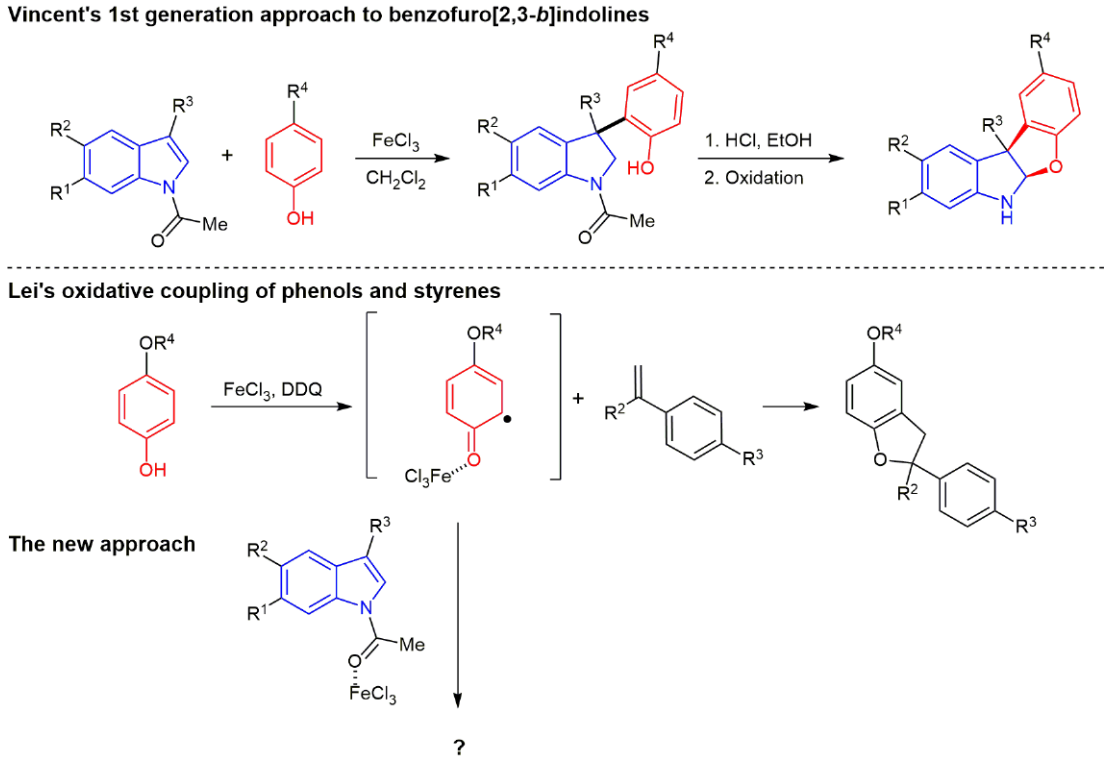
Coupling of Indoles and Phenols under Oxidative Conditions for the Synthesis of Benzofuro[3,2-*b*]indolines

Angew. Chem. Int. Ed. **2014**, *53*, 11881–11885

The group of Dr. Guillaume Vincent at the Institut de Chimie Moléculaire et des Matériaux d'Orsay (ICMMO) of Université Paris-Sud and CNRS (France) has been interested over the last four years in the development of new synthetic methods towards benzofuroindoline-containing frameworks which can be found in about a dozen natural products. "Their biosynthesis implies the oxidative coupling of indoles and phenols," explained Dr. Vincent. "In most cases this biogenetic annulation leads to the formation of a C–C bond between the C3- and *ortho*-positions of the indole and of the phenol, respectively, as well as a C–O bond between the C2-position of the indole and the oxygen of the phenol." Diazonamide A is the most famous compound of this family of benzofuro[2,3-*b*]indoline-containing natural products, displaying highly promising anticancer activities. "Interestingly, to date, only one natural product, called phalarine, displays the regioisomeric benzofuro[3,2-*b*]indoline skeleton," said Dr. Vincent. The synthesis of benzofuro[3,2-*b*]indolines has been studied extensively. "One of the main achievements in this field is the biomimetic total synthesis of diazonamide A by Harran and co-workers (*Angew. Chem. Int. Ed.* **2003**, *42*, 4961)," acknowledged Dr. Vincent, "which relied on the hypervalent iodine mediated oxidation of a phenol and the intramolecular trapping of the resulting phenoxenium intermediate by a nucleophilic indole." He continued: "Other methods which take advantage of the nucleophilicity of the C3-position of indoles have also been reported. However, we felt that complementary and general methods to access these heterocycles

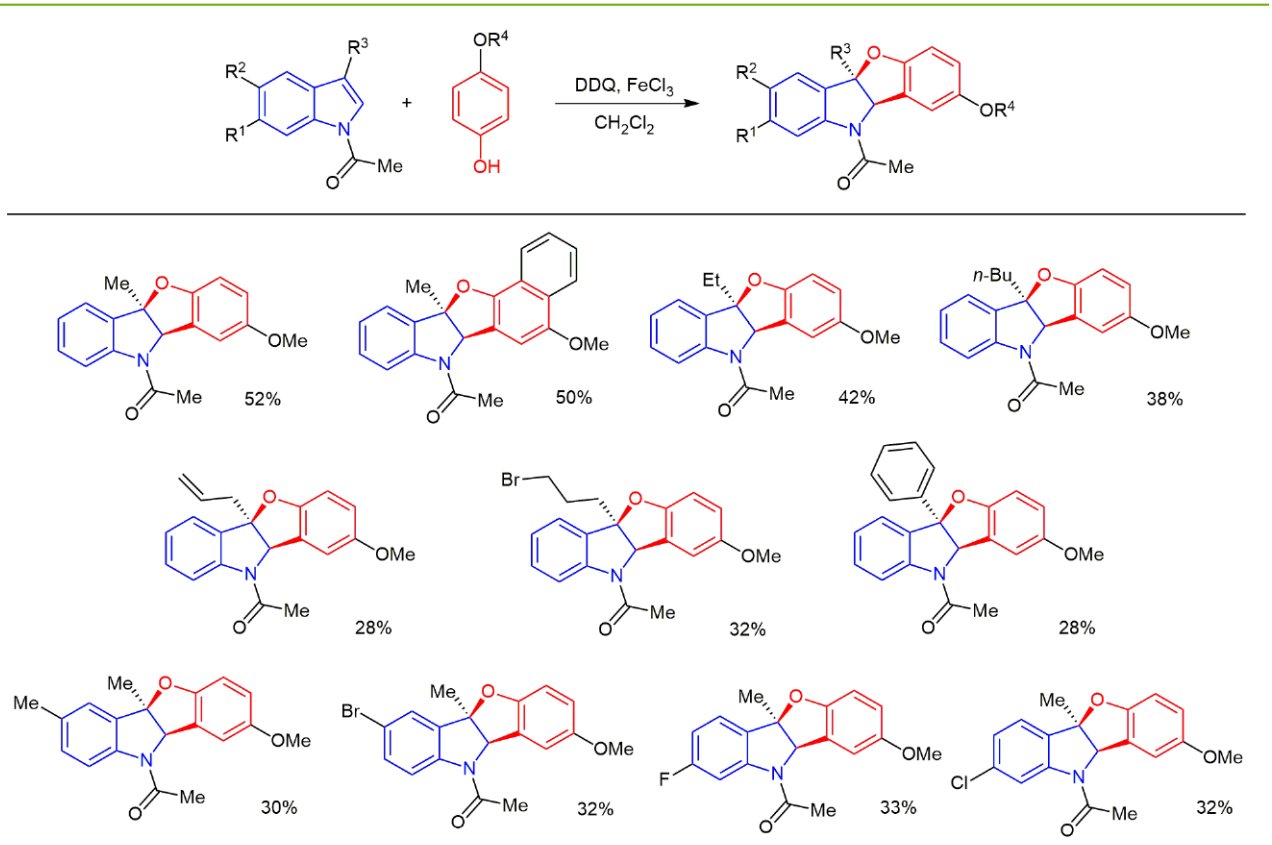


Scheme 1

SYNFORM, 2015/02
Published online: 19.01.2015, **DOI**: 10.1055/s-0034-1379741

were needed." In 2012, Dr. Vincent's team reported a two-stage strategy towards benzofuro[3,2-*b*]indolines related to diazonamide A (Scheme 1), involving a hydroarylation reaction of *N*-acetyl indoles by phenols mediated by $FeCl_3$, followed by an oxidation (*Angew. Chem. Int. Ed.* **2012**, *51*, 12546; *Chem. Eur. J.* **2014**, *20*, 7492). "The first stage features an umpolung of the indole, since in the hydroarylation step the heterocyclic nucleus became electrophilic at its C3-position, which is very unusual," said Dr. Vincent.

Professor Vincent continued: "Eager to improve our process, we wished to develop a one-step oxidative coupling between *N*-acetyl indoles and phenols. At this time, we came across a report from Lei and co-workers (*Angew. Chem. Int. Ed.* **2013**, *52*, 7151) that described the [3+2] oxidative coupling of phenols and styrenes or alkylalkenes mediated by DDQ and catalyzed by $FeCl_3$." Addition of a carbon-centered quinone radical, activated by $FeCl_3$, to the styrene was invoked (Scheme 1). Indeed, Dr. Vincent and co-workers were interested to see if a similar carbon-centered quinone radical could add to *N*-acetyl indoles activated by $FeCl_3$. After some experimentation, PhD student Terry Tomakinian was delighted to find that the treatment of *N*-acetyl indoles and phenols with stoichiometric amounts of DDQ and $FeCl_3$ allowed the synthesis of tetracyclic heterocycles (Scheme 2). "At first, we thought that we had made the desired benzofuro[3,2-*b*]indolines, since ^{1}H NMR spectra and mass spectrometry analyses seemed consistent," explained Dr. Vincent. "However, when looking more closely at the ^{13}C NMR spectra, we noticed some inconsistencies." The expected chemical shifts of about 55 ppm (C–C–C) and 110 ppm (N–C–O) for the carbons at the junction of the indole and the phenol were missing. Instead, chemical shifts of about 90 ppm (C–C–O) and 70 ppm (C–C–N) were observed, which are consistent with the regioisomeric benzofuro[3,2-*b*]indolines. Professor Vincent continued: "Eventually, Terry Tomakinian was able to obtain crystals of some of our compounds, and Dr. Régis Guillot was able to resolve their structures by X-ray crystallography and confirmed that we had indeed obtained benzofuro[3,2-*b*]indolines related to phalarine." The Paris-based researchers also thought that their compounds were contami-



Scheme 2

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nated with a small amount of impurities until they realized that two rotamers of benzofuro[3,2-*b*]indolines were present in the $CDCl_3$ solution in a ratio of about 4:1 because of the slow rotation around the N–(CO) bond of the *N*-acetyl. The ratio was almost 1:1 in DMSO at room temperature. Upon heating the DMSO-d_6 solution, disappearance of the rotamers was noticed. "The yields may seem modest but the complexity of the transformation should be taken into account!" said Dr. Vincent.

"To conclude, we have developed an unprecedented oxidative coupling between the indole and phenol nuclei that allows the synthesis of benzofuro[3,2-*b*]indolines," said Dr. Vincent. "The reaction proceeds by the oxidation of the phenol into a radical intermediate. We believe that the $FeCl_3$ promoter is crucial for the success of the reaction since it activates both the quinone radical and the *N*-acetyl indole. We also believe that the association of $FeCl_3$ and the carbonyl of the *N*-acetyl indole results in the decrease of electronic density on the indole nucleus. We are still pursuing the design of new methods towards benzofuroindolines (*Org. Lett.* **2014**, *16*, 5752) as well as the investigation of new reactive modes of indoles."

Matteo Zanda

About the authors

T. Tomakinian

Terry Tomakinian was born in Marignane (France) in 1988. After completion of his Bachelor's degree in organic chemistry from Université Aix-Marseille III (France) in 2009, he moved to ENSC Rennes (France) to obtain an engineering degree and an MSc degree in 2012. He carried out an internship at Oxford University (UK) supervised by Professor Stephen G. Davies in 2012. He is currently completing his PhD at Université Paris-Sud with Dr. Guillaume Vincent on the development of new methodologies towards the synthesis of benzofuroindolines.

Prof. C. Kouklovsky

Cyrille Kouklovsky was born in Paris (France) and educated at Université Paris-Sud. He defended his PhD in 1989 under the supervision of Professor Yves Langlois (CNRS, Gif-Sur-Yvette, France), working on the cationic asymmetric Diels–Alder reaction. He then took up a postdoctoral position in Professor Steven V. Ley's research group (University of Cambridge, UK), working on the total synthesis of rapamycin. In 1995, he was appointed as a "Chargé de Recherche" CNRS at Université Paris-Sud, working on asymmetric dipolar cycloaddition reactions and their synthetic applications. He was promoted to Professor of Chemistry in 2003. His research interests are in the fields of synthetic methodology, asymmetric synthesis and peptide synthesis.

Dr. G. Vincent

Guillaume Vincent was born in 1978 in Lyon (France). He graduated in 2002 from the Ecole Supérieure de Chimie Physique et Electronique de Lyon (CPE Lyon). During this period he spent one year at the Dupont Pharmaceuticals Company in Wilmington (USA) working with Dr. Patrick Y. S. Lam on the copper-catalyzed cross-coupling between boronic acids and NH-containing substrates. In 2002, he also obtained his MSc degree from Université Lyon I in the group of Professor Marco A. Ciufolini. He completed his PhD in 2005 under the supervision of Professor Ciufolini where he achieved the synthesis of the macrocycle of soraphen A. He then joined Professor Robert M. Williams at Colorado State University (USA) as a postdoctoral associate where he completed the total synthesis of cribrostatin IV. At the beginning of 2007 he returned to France in the group of Professors Max Malacria and Louis Fensterbank at the Université Pierre et Marie Curie - Paris 6 to study anionic-radical tandem reactions. Finally, at the end of 2007 he was appointed "Chargé de Recherche" by the CNRS at the Institut de Chimie Moléculaire et des Matériaux d'Orsay at Université Paris Sud working on nitroso-Diels–Alder cycloadditions and total syntheses of natural products. In 2011, he launched an independent research program towards the synthetic applications and understanding of unusual reactivities of the indole nucleus.

SYNFORM, 2015/02
Published online: 19.01.2015, **DOI**: 10.1055/s-0034-1379741