Organic LETTERS

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

Letter

pubs.acs.org/OrgLett

[Copper(I)(Pyridine-Containing Ligand)] Catalyzed Regio- and Steroselective Synthesis of 2-Vinylcyclopropa[*b*]indolines from 2-Vinylindoles

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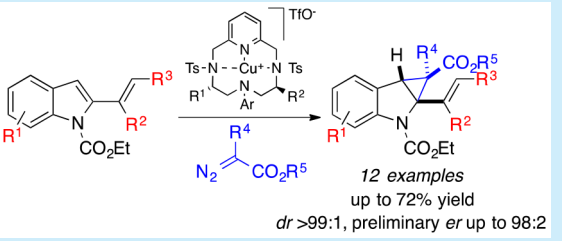
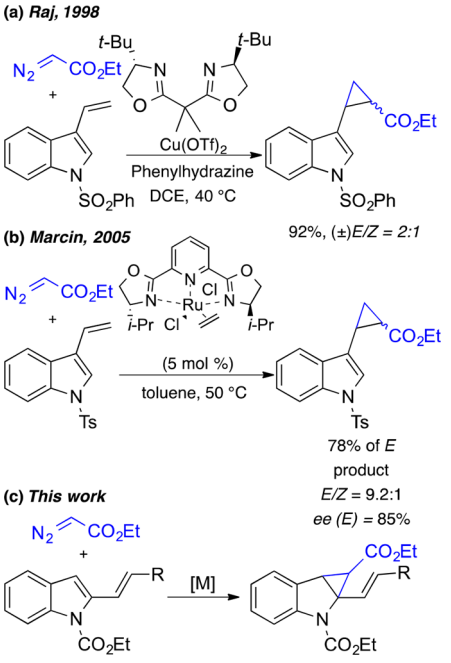
Supporting Information

ABSTRACT: A [copper(I)pyridine-containing ligand]-catalyzed reaction between 2-vinylindoles and diazo esters is described. The reaction allows for the synthesis of a series of 2-vinylcyclopropa[*b*]indolines with excellent levels of regio- and sterocontrol under mild conditions.



The introduction of a cyclopropane unit into a carbo- or heteroaromatic scaffold certainly represents an attractive challenge in synthetic organic chemistry.[1] While on the one hand, the cyclopropane ring itself is an important motif in medicinal chemistry,[2] on the other side, its manipulation gives access to other functionalities via ring opening and/or ring expansion.[3] Among the synthetic possibilities for generating a cyclopropane ring, intermolecular cyclopropanation by metal-catalyzed reactions with diazo compounds have been described for different electron-rich heterocycles including furans,[4] pyrroles,[5] and indoles.[6] Besides indoles, vinylindoles could also represent an interesting substrate for cyclopropanation. Thus, cyclopropanation at the C2−C3 bond of the indole nucleus could give rise to a new class of dearomatized indoles containing a vinyl-cyclopropyl moiety able to undergo further transformations.[7] However, vinylindoles have been seldom involved in cyclopropanation reactions with diazo esters and cyclopropanation regioselectively occurs at the exocyclic double bond. For example, in 1998, Raj and co-workers proposed the synthesis of 3-cyclopropylindoles by reacting *N*-sulfonylated 3-vinylindoles with ethyl diazoacetate (EDA) in the presence of a bisoxazoline copper(II) catalyst (Scheme 1a),[8] while more recently Marcin and co-workers proposed an asymmetric version of the same reaction using a chiral pyBox-ruthenium(II) complex (Scheme 1b).[9] In both these reports, cyclopropanation occurred at the external double bond of 3-vinylindole and, in addition, only 3-vinylindoles were tested under the optimized reaction conditions. Therefore, considering our interest in metal catalyzed synthesis and functionalization of indoles and indole derivatives,[10] we decided to verify the reactivity of 2-vinylindoles with EDA under metal catalysis (Scheme 1c). In particular, we wanted to selectively address the synthesis of a new class of dearomatized indoles, which could represent a useful intermediate in the synthesis of more complex molecules,[11] by cyclopropanation at C2−C3 indole.

Scheme 1. Reactions of Vinylindoles with EDA



Thus, 2-vinylindole **1a** and ethyl diazoacetate **2a** were reacted in a model reaction under various catalytic conditions.

Received: November 29, 2017

DOI: 10.1021/acs.orglett.7b03704
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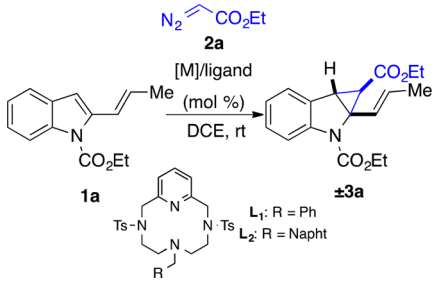
Some selected results are summarized in Table 1 (see SI for complete optimization report).

Table 1. Optimization of reaction conditions



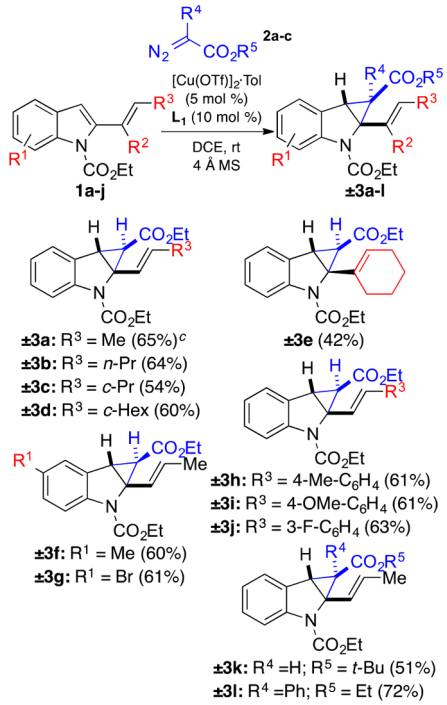
entry[a]	[M]/ligand	time, h	3a, (%)[b]
1	$[Cu(OTf)]_2$·Tol (2.5 mol %)	3	10
2	$[Rh(OAc)_2]_4$ (2.5 mol %)	3	<10
3	$[Cu(OTf)]_2$·Tol (2.5 mol %) L_1 (5 mol %)	3	43
4	$[Cu(OTf)]_2$·Tol (2.5 mol %) L_2 (5 mol %)	3	19
5	IPrCuCl (5 mol %), $NaBAr_F$ (5 mol %)	3	n.r.
6	$[Cu(OTf)]_2$·Tol (5 mol %) L_1 (10 mol %)	12	68[c]

[a]Unless otherwise mentioned, all reactions were carried out using **1a** (0.2 mmol) and **2a** (0.3 mmol) in DCE (0.1 M). EDA was added with a syringe pump at 0.5 or 0.17 mL/h. [b]Isolated yield. [c]**2a** (0.5 mmol), DCE (0.07 M) and 200 mg of 4 Å MS were added. IPr = 1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene.

At the outset, we selected copper(I) triflate and rhodium(II) acetate as best possible catalysts for our reaction. In fact, the corresponding carbene complexes have been widely used in this kind of transformations.[12] However, very poor yield of ±**3a** was observed with copper(I), while rhodium(II) afforded only traces of the desired product. In both cases, unreacted **1a** was recovered besides other products arising from the dimerization of **2a**. We moved next to other Cu(I) species, in particular we tested some complexes having a pyridine-containing macrocycle as ligand (L_1–L_2)[13] and showing enhanced solubility and stability compared to simple CuOTf. Moreover, these complexes were successfully applied as ligands in copper-catalyzed cyclopropanation reactions and Si–H carbene insertions.[14] Therefore, when the reaction between **1a** and EDA (**2a**) was conducted in the presence of $[Cu(I)L_1]OTf$, generated *in situ* from $[Cu(OTf)]_2$·Tol and the corresponding ligand L_1, the yield was significantly increased up to 43% (entry 3). 2-Vinylcyclopropa[*b*]indoline ±**3a** was formed as single regio- and diasteroisomer and its structure, as well as the relative position of the substituents around the cyclopropane ring, was completely elucidated by mono and bidimensional NMR analyses (see SI). Similarly, we verified the activity of another complex, namely the $[Cu(I)L_2]$ complex, but the yield of ±**3a** was strongly reduced (entry 4), while another copper(I) complex such as IPrCuCl/$NaBAr_F$ failed to give the desired product (entry 5). Finally, we found that doubling the catalyst loading to 10% and working with an excess of **2a** in the presence of 4 Å MS led to ±**3a** in 68% yield (entry 6). Having the best conditions, we next explored the scope of our transformation (Scheme 2).

The copper-catalyzed reaction between various 2-vinylindoles **1a–j** and diazoesters **2a–c** tolerated a wide substituent pattern and the formation of products ±**3a-l** was successful in all tested reactions. In particular, when we reacted *β*-alkyl substituted 2-vinylindoles bearing alkyl chain longer than

Scheme 2. Scope of the Reaction between 1 and 2[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.5 mmol) in DCE (0.07 M) and with 4 Å MS. Isolated yields. [c]Reaction performed on 2 mmol scale.

methyl, as well as secondary cyclic alkyl groups, products ±**3b–d** were formed in good and reproducible yields. In addition, the synthesis of ±**3a** could also be performed on higher scale without any substantial difference in the reaction yield. Then, a 2-vinylindole having an endocyclic vinyl moiety was employed, affording indoline ±**3e**, even if in lower yield, probably because of the steric hindrance at the side chain. We could use as starting material also indoles substituted on 5-position with electron-donating or electron-withdrawing groups, obtaining ±**3f** and ±**3g** in 60% and 61% yield, respectively. Then, we tested *β*-aryl substituted 2-vinylindoles and we verified that the presence of an aromatic ring did not influence the reaction outcome, and products ±**3h–j** were prepared efficiently. Besides EDA, other diazo compounds were tested under standard reaction conditions. The use of *t*-butyl diazoacetate (**2b**) afforded the desired product ±**3k** in 51% yield, while when we employed the *α*-disubstituted diazo compound **2c**, indoline ±**3l** was obtained in high yield as a single isomer.

Considering these results we decided to explore the possibility of developing an enantioselective synthesis of cyclopropanindolines **3** by using chiral ligands.[13b] To this scope, chiral pyridine-containing macrocycles L_3–L_5, as well as a chiral bisoxazoline, were employed in some preliminary test reactions (Scheme 3, see SI for further details).

First, we performed a brief screening of ligands for the synthesis of **3a**. In general, excellent results in terms of enantioselectivity were obtained by using L_3 and L_4, bearing two isopropyl groups on the macrocycle. However, in both cases, the yields resulted to be lower compared to the one achieved with L_1. Other ligands, such as monosubstituted macrocycle L_5 and chiral bisoxazoline ligands gave worse *er*. The activity of L_3 was evaluated with other vinylindoles as well

DOI: 10.1021/acs.orglett.7b03704
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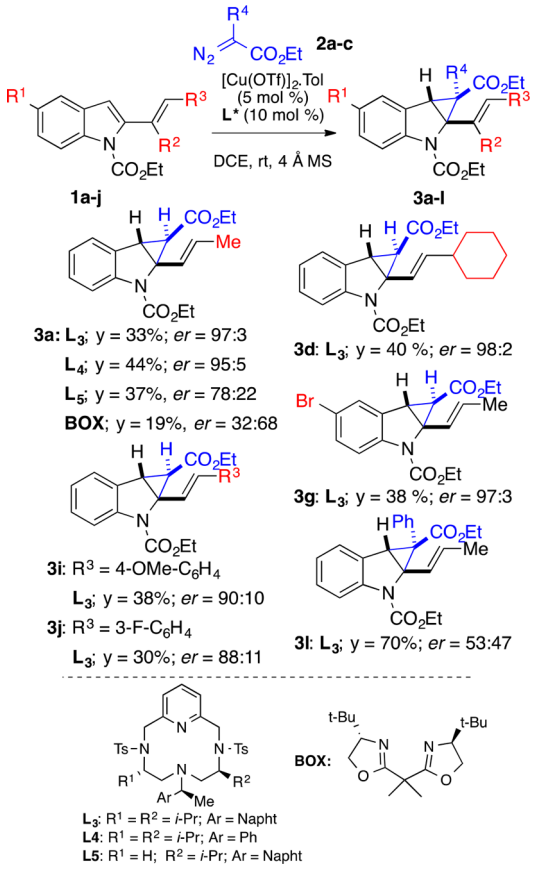
Scheme 3. Enantioselective Synthesis of 3[a]

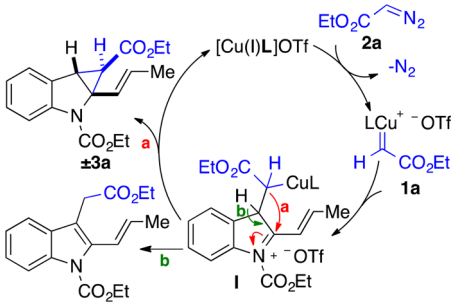


[a]Reaction conditions: **1** (0.2 mmol), **2** (0.5 mmol) in DCE (0.07 M) and with 4 Å MS. Isolated yields. HPLC was measured on pure isolated product.

and, similarly to before, it afforded from good to excellent levels of enantioselection despite the moderate yields of the resulting indolines. On the other hand, when we employed α-phenyl diazoacetate **2c** instead than EDA (**2a**), we were able to isolate **3l** in 70% yield but we completely lost the enantioselectivity of the process. A further optimization, in order to improve general yields and enantioselectivity in the case of α-substituted diazoester, is now on going in our laboratory.

The mechanism we propose for the synthesis of 2-vinylcyclopropa[*b*]indoline ±**3a** is illustrated in Scheme 4. After formation of the copper carbene complex from EDA and [Cu(I)**L**]OTf, nucleophilic attack of indole via C3 position leads to iminium cation **I** as intermediate. Because of the presence of an electron-withdrawing group on indole nitrogen,

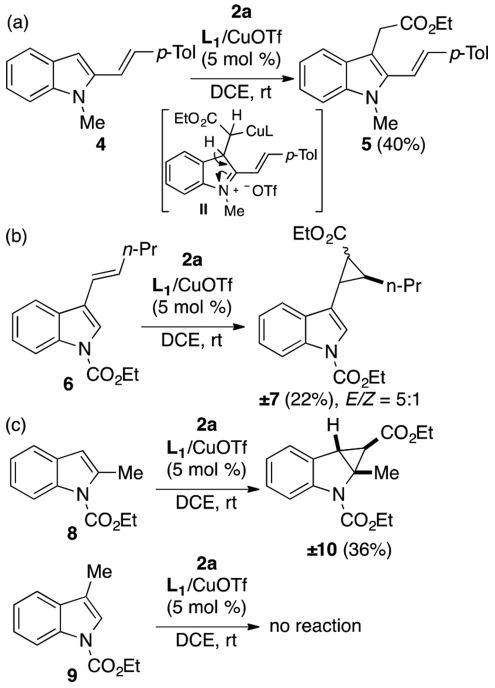
Scheme 4. Proposed Reaction Mechanism



iminium derivative **I** is highly electrophilic and can be quickly trapped by the nucleophilic carbene carbon atom leading to the stereoselective formation of the cyclopropyl ring (Scheme 4, path a). Formation of the cyclopropane ring is faster than the rearomatization process, which could give rise to C-3 alkylated indoles (Scheme 4, path b).[15]

To achieve some insights on our mechanistic hypothesis, we performed additional experiments modifying the nature and the position of the substituents at the starting indole. At first, we decided to investigate the role of the substituent on the indole nitrogen by introducing an electron-donating group in this position. Nevertheless, the reaction of *N*-methyl-2-vinylindole **4** with EDA yielded the hydroarylated indole **5** as single product (Scheme 5a). This compound arises from intermediate **II**,

Scheme 5. Additional Performed Experiments



analogous but relatively more stable than intermediate **I** in Scheme 4.[16] Thermodynamically favored indole **5** is thus formed instead of cyclopropa[*b*]indoline ±**3**. Moreover, 3-vinylindole **6**, tested under optimal reaction conditions, afforded an *E*/*Z* mixture of 3-cyclopropylindolines ±**7** in quite low yield (Scheme 5b). Thus, when the nucleophilicity of C3 diminishes, for inductive or resonance substituent effects, the cyclopropanation at C2−C3 of the indole is inhibited and the exocyclic double bond is involved in the cyclopropanation reaction.[8,9] Finally, we decided to test 2-methyl- and 3-methyl-*N*-ethoxycarbonylindoles **8** and **9** under optimal reaction conditions (Scheme 5c). The behavior of these derivatives parallels what observed with the corresponding vinylindoles **1** and **6**, yielding the C2−C3 cyclopropanation adduct using **8** as substrate; whereas **9** was recovered unaltered at the end of the reaction.

In conclusion, we report the first diastero- and enantioselective synthesis of 2-vinylcyclopropa[*b*]indolines by reaction of 2-vinylindoles with metal copper−carbene complexes having pyridine-containing macrocycles as ligands. The proposed method tolerated a broad range of substituents on the indole moiety and the use of various diazoacetates. Further develop-

DOI: 10.1021/acs.orglett.7b03704
Org. Lett. XXXX, XXX, XXX−XXX

ments of this work will be directed toward the improvement of the reaction yield and of the expansion of the reaction scope when chiral $\mathbf{L_3}$ is employed, as well as in the application of the obtained 2-vinylcyclopropa[*b*]indolines in other transformations involving the modification of the vinylcyclopropane ring.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03704.

Experimental procedures, characterization data and copies of ^{1}H and ^{13}C NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank *MIUR*-Italy (postdoctoral fellowship to V.P., Ph.D. fellowships to E.B and G. T.) for financial support. D. Nava and G. Celentano (University of Milan) are acknowledged for some NMR, mass, and HPLC analyses. We are grateful to Prof. E. Rossi, Prof. A. Caselli (University of Milan) and to Prof. R. Vicente (University of Oviedo) for helpful discussions.

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DOI: 10.1021/acs.orglett.7b03704
Org. Lett. XXXX, XXX, XXX−XXX