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A Synthesis of Multifunctionalized Indoles from [3 + 2] Annulation of 2-Bromocyclopropenes with Anilines

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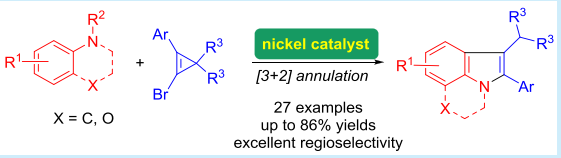
Supporting Information

ABSTRACT: A new regioselective method for the synthesis of multifunctionalized indoles from [3 + 2] annulation of 2-bromocyclopropenes with anilines has been developed. By employing a nickel complex as a catalyst, 27 examples of indole products were obtained in good yields with excellent regioselectivity. Synthetic utility of the resulting product was demonstrated in a concise synthesis of biologically active compound Paullone.



The indole unit is one of the most important structural components that is present in abundant natural products and drug molecules.[1] 2,3-Disubstituted indoles are very important synthetic intermediates that could be further transformed to various biologically active compounds, such as Paullone, Kenpaullone, and Cilansetron (Figure 1).

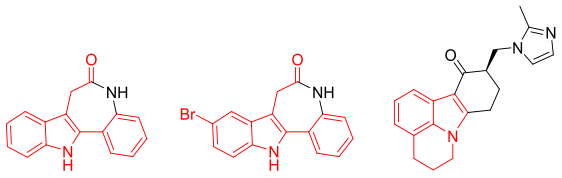
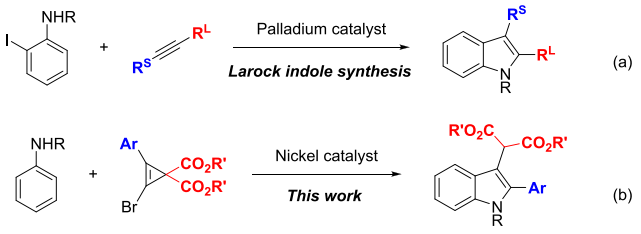


Figure 1. Indole containing biologically active compounds.

Paullone, Kenpaullone, and their analogues are potent inhibitors of the cyclin-dependent kinases (CDKs) and glycogen synthase kinase-3β (GSK-3β), which have become promising agents for the treatment of neurodegenerative and proliferative disorders.[2] Cilansetron is a 5HT-3 antagonist, considered as a promising drug to treat irritable bowel syndrome (IBS).[3]

The synthesis of multifunctionalized indole and their derivatives arouses intense interest from chemists.[4] New generations of more efficient and more practical indole synthesis methods continue to emerge.[5] For example, the Fischer indole synthesis, developed in 1883, has proven to be one of the most powerful routes.[6] Recently, instead of using carcinogenic hydrazines, by employing more readily available imines and enamines, the cross-dehydrogenative coupling strategy was developed for the synthesis of indoles by palladium catalysis.[7] Another example is the classic Bischler indole synthesis, which was first reported in 1892.[8] In modern synthesis, remarkable developments in the Bischler indole synthesis have been achieved involving N−H insertion reaction from diazo compounds with anilines,[9a] as well as the Ru(0) or Zn(II) catalyzed Bischler indole synthesis of propagylic alchols with anilines.[9b] In 1991, Larock and co-workers developed a palladium catalyzed regioselective formation of 2,3-disubstituted indoles by employing internal alkynes with 2-iodoaniline.[10] In a Larock indole synthesis, the aryl group of the aniline prefers to attach to the less bulky end (R^S) of the triple bond while the nitrogen moiety is more liable to assemble on the sterically more hindered end (R^L) (eq a, Scheme 1). Since

Scheme 1. Synthesis of 2,3-Disubstituted Indoles with Anilines and Alkynes or Cyclopropenes



the 2,3-disubstituted indole is a key structural motif of various biologically active natural and unnatural molecules, the synthetic methods that provide the 2,3-disubstituted indoles with an alternative regioselectivity is still highly in demand.

Cyclopropenes, as the smallest unsaturated cyclic molecule, exhibit a unique chemical property.[11] The vinylic carbon atoms of cyclopropene are $sp^{1.19}$ hybridized,[11d] indicating that the cyclopropane sometimes could serve as an alkyne equivalent.

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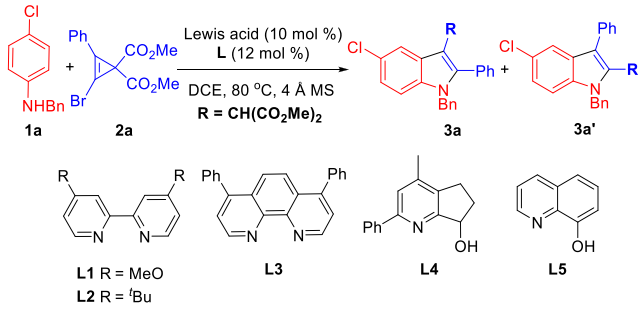
With continuing effort and interest in the field of both indole derivatives[12] and small ring compounds,[13] in this study, we have developed an unexpected synthesis of 2,3-disubstituted indoles from [3 + 2] annulation of donor−acceptor cyclopropenes[14,15] with anilines, which displays different regioselectivity, compared with the Larock indole synthesis, for the larger diester moiety to be installed at the 3-position and the smaller aryl group to be placed at the 2-position of indole (eq b, Scheme 1). In the presence of nickel(II) as the catalyst, various multifunctionalized indoles were furnished in up to 86% yield with excellent regioselectivities. Herein, we report the preliminary results.

Initially, we employed a bipyridine−Lewis acid complex as the catalyst to start our investigation of the [3 + 2] annulation of *N*-Bn-4-chloroanliline (**1a**) and dimethyl 2-bromo-3-phenylcyclopropene-1,1-dicarboxylate (**2a**).[16] As shown in Table 1, by using 10 mol % of $Ni(ClO_4)_2{\cdot}6H_2O$ as a Lewis acid and bipyridines as the ligand, both **L1** and **L2** gave the corresponding product **3a** in poor yields with moderate regioselectivities (23−25% yields, 6/1−5/1 rr, entries 1−2). With a phenanthroline type ligand **L3**, the 2,3-disubstituted indole was obtained in 23% yield with 5/1 rr after 45 h (entry 3).

Table 1. Optimization of the Reaction Conditions[a]



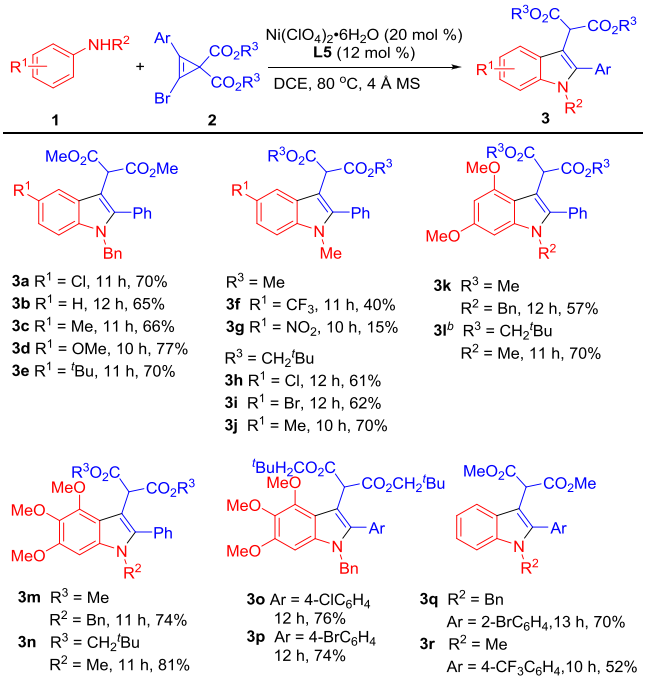
entry	Lewis acid	L	*t* (h)	rr	yield (%)[b]
1	$Ni(ClO_4)_2{\cdot}6H_2O$	**L1**	45	6/1	23
2	$Ni(ClO_4)_2{\cdot}6H_2O$	**L2**	45	5/1	25
3	$Ni(ClO_4)_2{\cdot}6H_2O$	**L3**	45	5/1	23
4	$Ni(ClO_4)_2{\cdot}6H_2O$	**L4**	24	5/1	43
5	$Ni(ClO_4)_2{\cdot}6H_2O$	**L5**	23	>20/1	50
6	$Cu(OTf)_2$	**L5**	25	>20/1	9
7	$FeCl_3$	**L5**	24	3/1	13
8	$Ga(OTf)_3$	**L5**	25	>20/1	13
9	$Ni(OTf)_2$	**L5**	25	>20/1	16
10[d]	$Ni(ClO_4)_2{\cdot}6H_2O$	**L5**	11	>20/1	70[c]

[a]The reactions were carried out under an Ar atmosphere with **1a** (0.6 mmol), **2a** (0.3 mmol), Lewis acid (10 mol %), **L** (12 mol %), and 4 Å MS (500 mg) in DCE (3 mL) at 80 °C. [b]NMR yield using 1,3,5-trimethylbenzene as the internal standard. [c]Isolated yield. [d]With 20 mol % of $Ni(ClO_4)_2{\cdot}6H_2O$. rr = regiomeric ratio = **3a**/**3a**′.

When an O,N-bidentate ligand **L4** was employed, the reaction was speeded up, providing **3a** in 43% yield with moderate regioselectivity after 24 h (entry 4). Notably, the commercially available 8-hydroxyquinoline was found to be the best ligand, leading to **3a** in 50% yield with >20/1 rr after 23 h (entry 5). Different metal salts, such as $Cu(OTf)_2$, $FeCl_3$ and $Ga(OTf)_3$, in combination of **L5** gave poor results (entries 6−8). Changing the counterion from perchlorate to triflate, the **L5**/nickel(II) catalyzed reaction lost efficacy and only resulted in 16% yield of **3a** (entry 9 vs 5). To our delight, with 20 mol % of $Ni(ClO_4)_2{\cdot}6H_2O$, the reactivity of the [3 + 2] annulation was increased to 70%, and the reaction time was shortened to 11 h (Table 1, entry 10).

Under the optimized reaction conditions, various aniline derivatives were reacted with cyclopropenes bearing different ester groups, affording good to high yields with excellent regioselectivites. As shown in Scheme 2, *N*-Bn-anilines containing different substituents, such as Cl-, Me-, MeO-, ^{t}Bu- at the para-position, could reacted smoothly, leading to the corresponding multifunctionalized indoles **3a**−**e** in 65−77% yields. *N*-Me-anilines were also suitable substrate, delivering the *N*-Me-indole derivatives **3f**−**j** in 61−70% yields, while anilines with a strong electron-withdrawing substituent such as CF_3 and NO_2 could also afford the desired products but with lower yields (**3f**−**g**). Multisubstituted anilines such as 3,5-dimethoxyanilines and 3,4,5-trimethoxyanilines were tolerated in the current catalyst system. In both cases, the *N*-Me-3,5-dimethoxyindoles **3l** and the *N*-Me-3,4,5-trimethoxyindoles **3n** were obtained in 70−81% yields. Furthermore, cyclopropenes bearing different substituents at both para- and ortho- positions of aryl groups (**3o**−**q**) also worked well, affording the corresponding indoles in 70−76% yields.

Scheme 2. Substrate Scope of Aniline Derivatives[a]



[a]Conditions in entry 10, Table 1; Isolated yields of **3**; With >20/1 rr in all cases unless noted. [b]With 11/1 rr. rr = regiomeric ratio.

The structure of **3a** was determined by the X-ray diffraction of the single crystal of the reaction product.[17] As shown in Figure 2, the phenyl group from the cyclopropene was installed at the 2-position of the indole product, while the diester moiety was located at the 3-position.

Remarkably, tricyclic indoles are also accessible through this [3 + 2] annulation reaction by using tetrahydroquinolines instead of anilines (Scheme 3). It is worth mentioning that tricyclic indoles are found as a core structure in many natural products and biologically active molecules, such as Cilanse-

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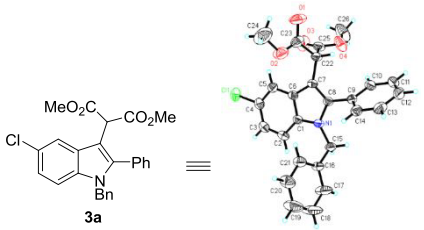
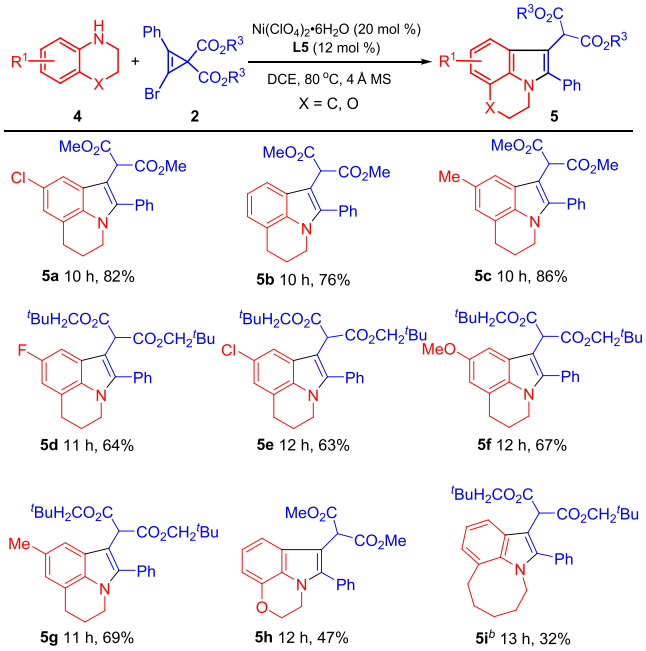


Figure 2. Crystal structure of **3a**.

Scheme 3. Substrate Scope of Tetrahydroquinoline Derivatives[a]



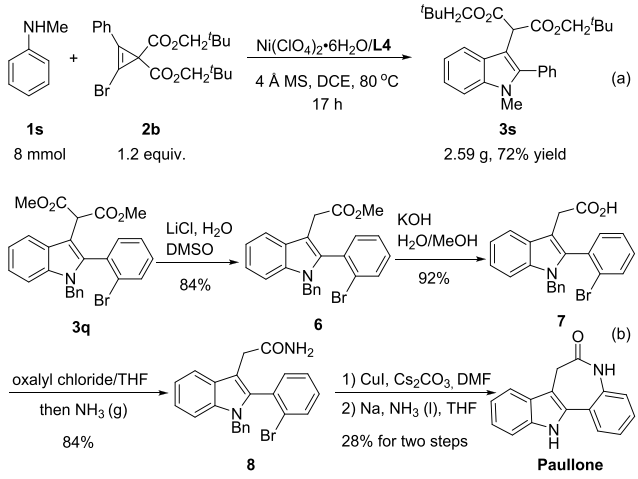
[a]Conditions in entry 10, Table 1; Isolated yields of **5**; With >20/1 rr in all cases unless noted. [b]**L4** was used with 10 mol % of $Ni(ClO_4)_2 \cdot 6H_2O$, **4i**/**2b** = 1/1.2; with 6.4/1 rr. rr = regiomeric ratio.

tron.[3,18] As shown in Scheme 3, various tetrahydroquinolines with both electron-donating and enlectron-withdrawing groups substituted at the aryl ring could give the corresponding tricyclic indoles **5a**−**g** in up to 86% yield with excellent regioeselectiviy. Benzomorpholine is also a suitable substrate and gave the corresponding tricyclic indole **5h** in moderate yield. Moreover, the reaction can be extended to a larger cyclic amine, giving product **5i** bearing an eight-numbered ring in 32% yield with 6.4/1 rr.

This method was found to be synthetically promising. As shown in Scheme 4a, a scaled-up reaction was carried out, and 2.59 g of indole **3s** were obtained in 72% yield. The synthetic utility of this reaction was further demonstrated in a concise synthesis of Paullone, which was a potent cyclin-dependent kinase inhibitor and tauprotein kinase inhibitor (Scheme 4b).[2a] The product **3q** was easily transformed to the monoester **6** by decarboxylation, which was then subjected to hydrolysis and amidation to give compound **8**. The Paullone was finally obtained after an intramolecular Ullmann type reaction[16] of compound **8** followed by deprotection of the benzyl group.

In conclusion, we have developed a new method for the regioselective synthesis of 2,3-functionalized indoles via [3 + 2] annulation of anilines and 2-bromocyclopropenes. In the

Scheme 4. Scaled-Up Reaction and Applications



presence of a nickel complex as the catalyst, a variety of anilines as well as tetrahydroquinolines were found as compatible substrates, providing versatile multifunctionalized indoles (27 examples) in high yields with excellent regioselectivity. The current method is practical and potentially synthetically useful, which was demonstrated in a scaled-up reaction and synthesis of Paullone. Further application of this reaction in the construction of indole alkaloids is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01276.

Experimental procedures and characterization data (PDF)

Accession Codes

CCDC 1014786 and 1909652 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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