

Indole Synthesis via Cyclative Formation of 2,3-Dizincindoles and Regioselective Electrophilic Trapping

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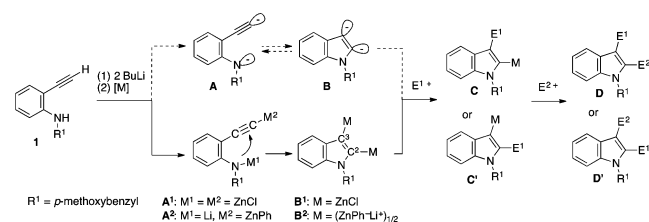
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S Supporting Information

ABSTRACT: Upon zincation of two acidic protons attached to the nitrogen and the sp-carbon atoms, a *N*-protected 2-ethynylaniline cyclizes to a 2,3-dizincindole at 120 °C. Driven by the energy gain due to formation of two C–Zn bonds, this reaction occurs smoothly without side reactions, although this transformation is intrinsically endothermic in its bare anionic form. The resulting dizinc intermediate can be functionalized with one or two different electrophiles either inter- or intramolecularly on either C² or C³ selectively, depending on the choice of catalyst and the electrophiles. This conversion of 2-ethynylaniline to 2,3-dimetalloindole can be applied to an expeditious synthesis of indenoindolone and benzodipyrrole derivatives, which are compounds of interest for medicinal chemistry and materials science, respectively.

1,2-Dimetalated aromatics have great potential for the synthesis of multisubstituted aromatic compounds, yet they have so far been useful only for introduction of two identical electrophiles.^{1,2} 2,3-Dimetalloindoles behave similarly,³ probably because a monometallic intermediate formed by the first electrophilic trapping (e.g., C in Scheme 1) is more reactive than the dimetallic

Scheme 1. Metalative Conversion of 2-Ethynylaniline (1) into a 2,3-Dimetalloindole and Polysubstituted Indoles



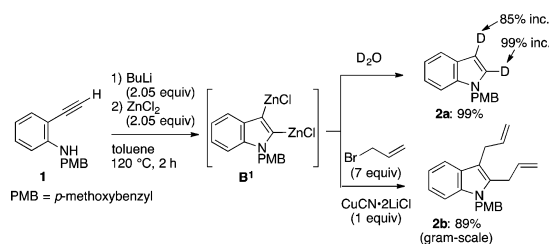
starting material (e.g., B), and they have so far not found much utility in the synthesis of substituted indoles, which are compounds of interest for medicinal chemistry⁴ and materials science.⁵ We report here the preparation and electrophilic trapping of 2,3-dizincindole compounds (**B**¹ and **B**² in Scheme 1)⁶ that allow us to achieve selective monofunctionalization at either C² or C³, or difunctionalization with the same or two different electrophiles depending on reactants and reaction conditions. The synthetic methodology described here provides access to a variety of 2-substituted, 3-substituted, and 2,3-disubstituted indoles and congeners, including a 5*H*-indeno[1,2-

b]-indol-10-one derivative of interest for cancer therapy⁷ and a benzodipyrrole derivative of interest as an organic semiconductor.⁵

Inspired by an indole synthesis⁸ through cyclization of a 2-alkynylanilide monoanion (as its zinc complex),⁹ we conjectured on cyclization of a dianion (A) of 2-ethynylaniline (1) to the corresponding vicinal dianion of 2,3-disubstituted indole (B), followed by electrophilic trapping to obtain a 2,3-disubstituted indole D. From an energetic point of view, conversion of A (R¹ = Me) to B per se is obviously unfavorable (30.6 kcal/mol endothermic; B3LYP/6-31G*+). In fact, a 2,3-dilithio complex of B (R¹ = PhSO₂) readily opens to A even at –100 °C, whereas it remains stable at –78 °C when R¹ is methyl.³ We found that the A-to-B conversion does occur quantitatively and irreversibly when the counteranions are Zn(II), and proposed a dimeric structure to rationalize the stability and selective reactions of the dizinc intermediate. 2,3-Dizincindoles **B**¹ or ate complexes **B**² thus formed exhibit synthetically useful reactivity and selectivity.

We describe first the cyclization of a zinc chloride intermediate **A**¹. As shown in Scheme 2, *N*-protected 2-ethynylaniline **1** was

Scheme 2. Cyclization of a 2-Ethynylaniline (1) into 2,3-Dizincindole (B¹)



deprotonated at the nitrogen and the terminal with 2 equiv of BuLi in hexane and then was treated with 2 equiv of ZnCl₂ in THF. Hexane and THF were removed under vacuum, and the residual white solid was dissolved in dry toluene under nitrogen. Upon heating at 120 °C in toluene for 2 h, the dizincio intermediate^{9,10} produced 2,3-dizincindole **B**¹ in quantitative isolated yield, as shown by quenching with deuterium oxide (D on C², 99%; on C³, 85%). Coupling with excess allyl bromide in the presence of a Cu(I) additive^{9b,11} gave diallylindole **2b** in 89% yield on a gram scale.

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It is remarkable that cyclization took place without any side reactions even though it was performed at a high reaction temperature. The reaction was much slower in a polar solvent such as THF, suggesting the importance of Zn(II)–alkyne interaction in the cyclization reaction. The thermal stability of the intermediate **B**¹ is also intriguing because of the potential reversibility of such a cyclization reaction.³ We used a removable *p*-methoxybenzyl group (PMB)¹² for the present study, whereas a simple benzyl group can be used equally well for cyclization and subsequent selective reaction with electrophiles (data not shown).

The stable zinc intermediate **B**¹ was found to produce a 3-substituted indole when reacted with simple electrophiles in accordance with the typical indole reactivity, a 2-substituted product under transition-metal catalysis, and a 2,3-disubstituted product through sequential electrophilic trapping (Scheme 2 and Table 1, entry 9). The monosubstitution reactions proceeded with high selectivity, but the product selectivity was lower, and disubstitution also proceeded to some extent.

Upon reaction with excess iodine, 2,3-diiodoindole was obtained as the main product, together with a small amount of 3-iodoindole (entry 1). The diiodo product also formed when we used 1 equiv of iodine. However, when we used 1 equiv of methyl iodide (entry 2) or aryl chloride (entry 3), the reaction took place selectively at C³ without formation of 2-substituted product. The methyl iodide reaction (entry 2) gave a small amount of 2,3-dimethylindole (6%) together with recovery of 2,3-unsubstituted indole (2, 7%). Interestingly, when these reactions were quenched with deuterium oxide, deuterium incorporation occurred quantitatively at both the C² and C³ positions of **2** (i.e., **2a**), indicating that the dizinc intermediate **B**¹ was left unreacted. **B**¹ is a rather unreactive nucleophile and was found not to add to ketones.

As shown in entries 4–6, a transition-metal catalyst switched the preferred regioselectivity in the reaction of **B**¹ from C³ to C². Thus, reaction of **B**¹ with an aryl chloride in the presence of a Pd catalyst¹³ predominantly gave 2-aryloindole (entry 4), the reaction with cyclohexyl iodide in the presence of an iron catalyst¹⁴ gave 2-alkylindole (entry 5), and the reaction with iodobenzene in the presence of a nickel catalyst gave 2-phenylindole (entry 6). These reactions proceeded with good C²-selectivity, whereas the iron-catalyzed reaction was less selective.

In the presence of a palladium catalyst,¹⁵ Negishi reaction¹⁶ with excess aryl (entry 7) or heteroaryl halide (entry 8) produced the corresponding 2,3-homodisubstituted indoles in high yield, together with a small amount of monosubstituted product. Interestingly, for the iron-, nickel-, and palladium-catalyzed reactions of aryl iodides (entries 5–8), we did not observe any deuterium incorporation upon quenching with deuterium oxide, whereas we observed the deuteration of **2** in the palladium-catalyzed aryloxylation (entry 4). As described in Scheme 2, the reaction of **B**¹ with excess allyl bromide in the presence of a Cu(I) additive¹¹ gave 2,3-diallylindole in high yield (entry 9).

The selective reaction of **B**¹ at C³ with aryl chloride or methyl iodide (entries 2 and 3) allowed us subsequently to functionalize the C² position with a different electrophile, such as iodobenzene under Pd catalysis (entries 10 and 11). Such regioselectivity allowed us to achieve five-membered ring annulation on an indole skeleton. For example, a thermal reaction of **B**¹ with 2-iodobenzoyl chloride at 110 °C produced a 5*H*-indeno[1,2-*b*]indol-10-one derivative (entry 12), a class of compounds of some medicinal interest.⁷ This reaction proceeds through the C³-

Table 1. Introduction of Various Electrophiles Using Dizincindole **B**^{1a}

entry	E ¹ , E ² (equiv)/cat	major product and yield ^{b,c,d}	byproducts and yield ^d
1	E ¹ : I ₂ (5.0) / – E ² : NH ₄ Cl	74%	7% nd ^f
2	E ¹ : MeI (1.2) / – E ² : D ₂ O	74%	6% 7%
3	E ¹ : (1.00) / – E ² : D ₂ O	73%	20%
4	E ¹ : (1.05) / Pd ^g E ² : D ₂ O	51%	14% 13%
5	E ¹ : CyI (7.0) / Fe ^h E ² : D ₂ O	47%	13% trace 19%
6	E ¹ : PhI (2.5) / Ni ⁱ E ² : D ₂ O	75%	4% 18%
7	E ¹ : R-I (2.5) / Pd ^j E ² : D ₂ O	87%	9% nd
8	R = 2-thienyl	67%	15% 6%
9	E ¹ : Br (4.0) / Cu ^k E ² : NH ₄ Cl	89%	8% nd
10	E ¹ : MeI (1.2) / – E ² : PhI (3.0) / Pd ^g E ³ : D ₂ O	64%	7% 4% 25% 6%
11	E ¹ : (1.05) / – E ² : PhI (2.5) / Pd ^g E ³ : D ₂ O	76%	5% 12% 5%
12	E ¹ = E ² : (1.2) / – then 110 °C E ³ : NH ₄ Cl	58%	5% 5%

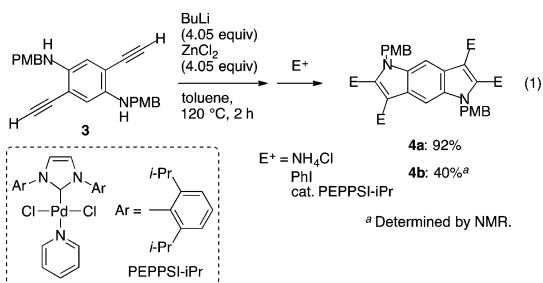
^aDizincindole **B**¹ was prepared as described in Scheme 2 on a 0.2–0.4 g scale (except entry 8, 4.2 mmol (1 g) scale), and then it was allowed to react with electrophiles as described in this table. See SI for details. ^bThe products shown refer to products upon D₂O quenching (except in entries 8, 9, 11), whereas the reaction yield and product structures were determined for the corresponding protio compounds. ^cThe C²/C³ regioselectivity (when applicable) for the major product was >99% for all entries, except entry 5. ^dThe yield for the major product is based on pure isolated protio product (except entries 5 and

Table 1. continued

6, NMR), and the yields of the byproducts are estimated by either isolation, GLC, or NMR analysis. ^end = not detected. ^f*p*-Anis = *p*-anisyl. ^gThe reaction proceeded in the presence of 5 mol % of Pd₂(dba)₃·CHCl₃/20 mol % of PPh₃. ^hThe reaction proceeded in the presence of 2 equiv of (trimethylsilyl)methylmagnesium chloride, 10 mol % of FeCl₂, and 2 equiv of TMEDA. ⁱThe reaction proceeded in the presence of 10 mol % of Ni(acac)₂/20 mol % of PPh₃. ^jThe reaction proceeded in the presence of 10 mol % of PEPPSI-*i*Pr (Pd). ^kThe reaction proceeded in the presence of 2 equiv of CuCN·2LiCl, then allyl bromide was added.

selective arylation path (cf. entries 3 and 11), followed by intramolecular reaction of the aryl iodide with the 2-zinc intermediate.¹⁷

Double cyclization of 2,5-diethynyl-1,4-phenylenediamine derivative **3** also proceeded in excellent yield to give a tetrazincobenzodipyrrole isolated after aqueous workup as unsubstituted benzo[1,2-*b*:4,5-*b'*]dipyrrole **4a** (eq 1), indicating



that the cyclization reaction tolerates substitution on the benzene ring. A tetrazinc intermediate of the reaction underwent 4-fold phenylation in 40% yield upon reaction with iodobenzene under palladium catalysis¹³ to give tetraphenylbenzodipyrrole **4b**, a potent hole-transporting material for optoelectronic applications.⁵ Partially phenylated products accounted for the rest of the material.

We next describe the preparation and reactions of a zincate intermediate, **B**². We found that the cyclization reaction also takes place by addition of only 1 equiv of Zn(II) via a putative Li/Zn-heterodimetallic intermediate **A**². Treatment of **1** with 2 equiv of BuLi followed by addition of 1 equiv of PhZnBr (to form **A**²), and, after removal of hexane and THF, heating at 120 °C in toluene for 2.5 h produced cyclization into the dimetallic intermediate **B**², as confirmed by quenching with deuterium oxide (Table 2, entry 1). Reaction by use of 1 equiv of ZnCl₂ also resulted in quantitative cyclization, confirmed after aqueous workup (SI), while the intermediate was entirely insoluble and synthetically useless, possibly because of the oligomeric or polymeric nature of the zinc intermediate.¹⁸

The reactivity of the zincate intermediate **B**² prepared from 1 equiv of PhZnBr was found to be markedly different from that of **B**¹ prepared from 2 equiv of ZnCl₂. For example, it added to diarylketones in good yield and only on the C³ position (entries 2 and 3), whereas the dizincindole **B**¹ hardly reacted with any ketones (SI). Chalcone also reacted exclusively at C³ to give a 1,4-addition product (entry 4). The reaction with aliphatic aldehydes and ketones was complicated and formed a variety of side products, including in situ loss of the oxygen group originating from the carbonyl group. Addition of benzophenone followed by allylation in the presence of a Cu(I) additive gave regioselectively a 2,3-disubstituted indole (entry 6). All of these reactions of **B**²

Table 2. Introduction of Various Electrophiles Using Intermediate **B**²

entry	E ¹ , E ² (equiv)/cat	major product and yield ^{b,c,d}	byproducts and yield ^d
1	E ¹ : D ₂ O E ² : D ₂ O	99% ^f	nd ^e
2	E ¹ : Ph-C(=O)-Ph (1.2) / - E ² : D ₂ O	76%	18%
3	E ¹ : Ph-C(=O)-C ₆ H ₄ -F (1.2) / - E ² : D ₂ O	77%	18%
4	E ¹ : Ph-CH=CH-C(=O)-Ph (1.2) / - E ² : D ₂ O	83%	5%
5	E ¹ : Me ₃ SnCl(1.2) / - E ² : D ₂ O	55%	40%
6	E ¹ : Ph-C(=O)-Ph (1.2) / - E ² : Br-CH ₂ -CH=CH ₂ (7.0) / Cu ^g E ³ : NH ₄ Cl	45%	38% trace 6% nd

B² was prepared by the reaction of **1** with 2 equiv of BuLi and 1 equiv of PhZnBr as described in the text and SI, on a 0.2–0.4 g scale. ^bThe products shown refer to products upon D₂O quenching (except in entry 6), whereas the reaction yield and product structures were determined for the corresponding protio compounds. ^cThe C²/C³ regioselectivity (when applicable) for the major product was >99% for all entries. ^dThe yield for the major product is based on pure isolated protio product, and the yields of the byproducts are based on either isolation, GLC, or NMR analysis. ^end = not detected. ^fDeuterium was incorporated 100% at C² and 91% at C³. ^gThe reaction proceeded in the presence of 1 equiv of CuCN·2LiCl, then allyl bromide was added.

with electrophiles occurred at C³ to produce a single regioisomer, and quenching with deuterium oxide indicated that the metallic intermediate was still present at the end of the reaction (i.e., after the consumption of electrophile).

Interestingly, the reaction of **B**² with chlorotrimethylstannane¹⁹ occurred selectively at C² to give a 2-stannyindole in good yield (entry 5). Chlorotrimethylsilane gave a C²-silylation product in only 9% yield. This and the reactivity described above suggest that the carbonyl addition and the stannylation reactions are not simple nucleophilic reactions but occur through electron transfer.²⁰

Finally, we discuss the structure of the zinc intermediates as correlated to the reactivity and regioselectivity of the observed reactions. The crystal structure of a structurally similar 2,3-dialuminoindole is known, for which we can draw the resonance scheme shown in Figure 1a.² We can similarly consider a dimeric structure for **B**¹ in Figure 1b, where ZnCl₂ groups are coordinated to the indole π-system to form a zwitterion, where the C³-carbon is tetrahedral whereas the C²-carbon is trigonal. Such a vicinal tetragonal/trigonal coordination is also known for a 1,2-

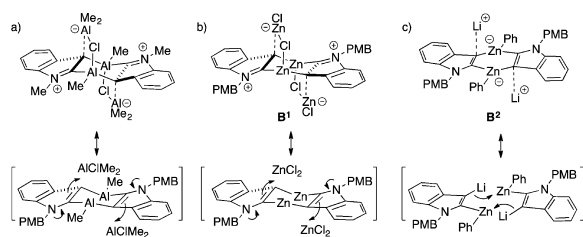


Figure 1. Structures of 2,3-dimetalated indoles. (a) Reported structure of 2,3-dialuminoindole.² (b) Plausible structure of intermediate B¹. (c) Plausible structure of intermediate B².

dimagnesiobenzene tetramer [(C₆H₄Mg)₄], which is not a very reactive nucleophile.¹⁸ We ascribe the low nucleophilicity of B¹ (e.g., to carbonyl compounds) to such a dimeric structure where the potentially nucleophilic C³-carbon is coordinated to two Lewis acidic metal atoms and hence is deactivated. When transition-metal catalysis is involved, the trigonal C²-carbon reacts preferentially with the catalyst to form a new C–C bond at C² (e.g., Table 1, entry 3 vs 4).

When we used only 1 equiv of PhZnBr, the cyclization generated a 2-zincio-3-lithioindole, which however dimerizes to give a zincate, as shown in Figure 1c. The C³-carbon in B² is expected to be more nucleophilic than the C³-carbon in B¹ as is experimentally observed (cf. Table 2).

In conclusion, the large energy barrier for the cyclization of dianion A to vicinal dianion B can be overcome by the use of zinc counteranions, and a dizincio 2-ethynylaniline smoothly cyclizes into a 2,3-dizincioindole without any side products. Subsequent electrophilic treatment provides a modular approach to expeditious synthesis of a variety of indoles, including 2,3-substituted derivatives, indenoindolone of medicinal interest and benzodipyrrole of materials interest. The present work not only adds to the synthetic repertoire of dimetallic compounds^{21,22} but also presents a rare example of the control of regioselectivity upon electrophilic trapping by the use of uncatalyzed or transition-metal catalyzed reaction conditions.^{5–8} The reaction mechanism where two metals cooperatively lower the energy barrier of the A-to-B cyclization, and the structural and synthetic chemistry of the bimetallic intermediate are intriguing subjects for future studies.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b10061.

Experimental details (PDF)

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Notes

The authors declare no competing financial interest.

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