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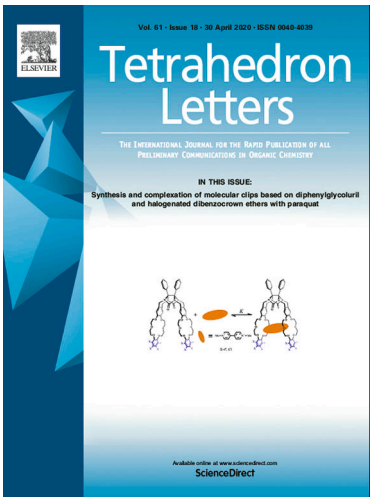

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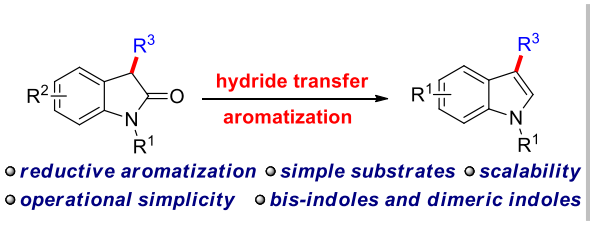

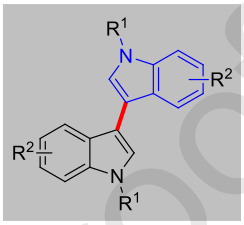

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Reductive aromatization of oxindoles to 3-substituted indoles

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ABSTRACT

A practical and scalable approach for the synthesis of 3-substituted indoles is delineated via hydride nucleophilic addition to 3-substituted-2-oxindoles. The reaction proceeds through reductive aromatization involving indolinium ion intermediate. A wide range of 3-functionalized indoles have been synthesized. The method is employed for the synthesis of 3,3′-bis-indoles and a dimeric 3-indole derivative. Moreover, this protocol is used to obtain naturally occuring amino acid tryptamine.

Indole is the most common and widely studied heterocyclic system. It is embodied in a myriad of natural products, pharmaceuticals and polymers [1]. The widespread natural occurrence of 3-substituted indoles in plants [2], fungi [3] and marine organisms [4] as well as their medicinal applications have stimulated continuing development of new methods for their preparation [5, 6]. The neurotransmitter amino acids like tryptophan [7], tryptamine [8], and serotonin contain the indole skeleton (Figure 1). In higher plants, degradation of tryptophan produces heteroauxin (indole-3-acetic acid), a plant hormone. Bufotenine is used as hallucinogens in humans. Marine indole alkaloids like (*E*)-methyl 3-(6-bromo-1H-indol-3-yl)acrylate have been extracted from a number of sponges [9-11]. Alkaloid (±)-chelonin A (Figure 1), isolated from a marine sponge of the *Chenolaplysilla* sp [12] show potent antimicrobial and anti-inflammatory activities. Similarly, discodermindol discovered in *discodermiapolydiscus* shows moderate cytotoxicity [13].

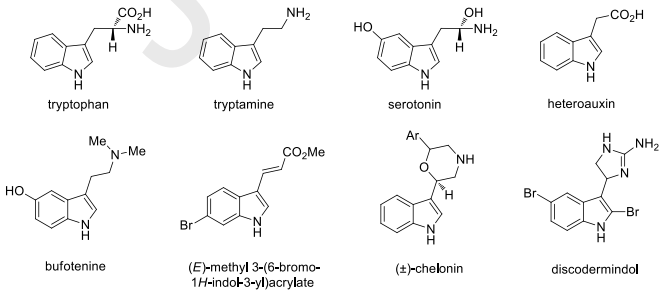
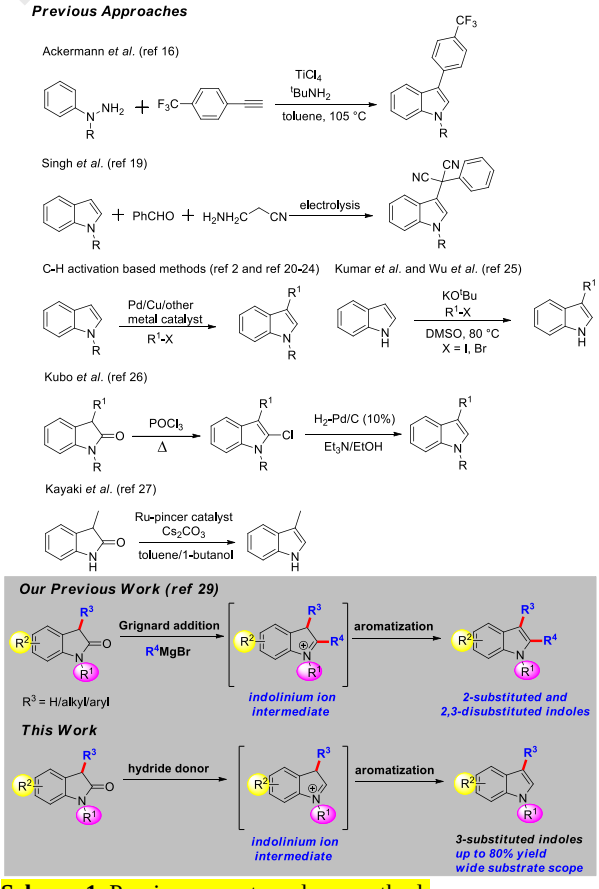


Figure 1. Some biologically important 3-indole derivatives.



Scheme 1. Previous reports and our method.

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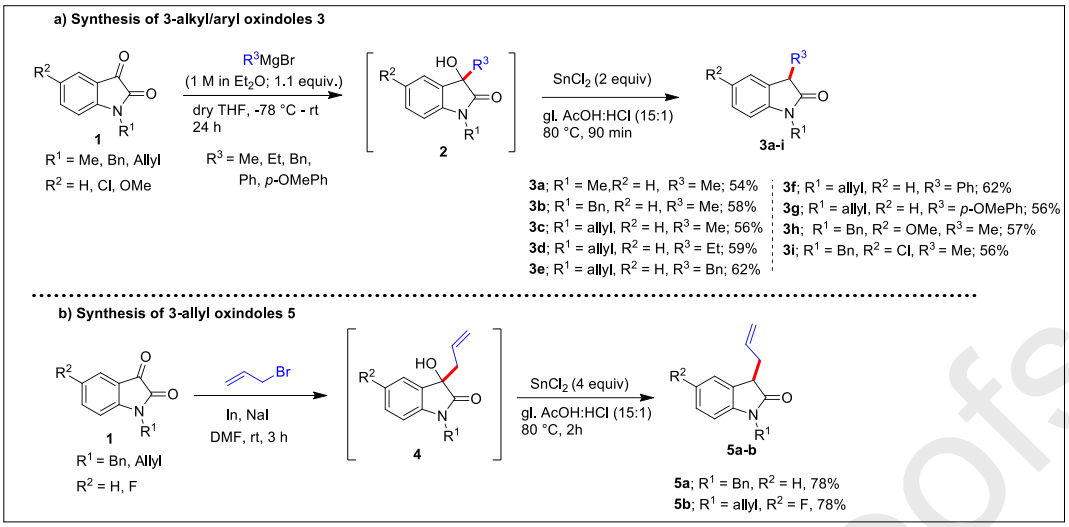


Scheme 2. Preparation of 3-substituted oxindole derivatives.

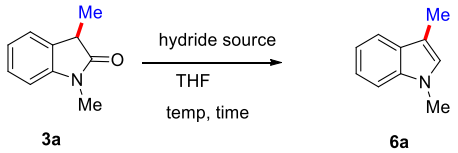
The classical Fischer indole synthesis remains one of the most important approaches to obtain 3-substituted indoles [14]. Since indole undergoes electrophilic substitution mainly on the C3-position, several methods like Friedel Crafts alkylation or acylation and Barbier type reaction have been developed over the years [15]. Recently, Ackermann and co-workers reported an efficient atom-economical method to synthesize C3-substituted indoles based on intermolecular titanium chloride catalyzed hydroamination of alkynes with hydrazine derivatives (Scheme 1) [16]. Kumar *et al.* developed Michael addition to synthesize 3-substituted indoles using $NbCl_5$ [17]. The preparation of various functionalized 3-indoles was also reported via the formation of reactive alkylideneindolenine intermediates [18]. Singh *et al.* developed an electrochemical multicomponent reaction involving indole, aldehyde and malononitrile for the construction of 3-functionalized indoles (Scheme 1) [19]. Over the last decade, C-H activation has also emerged as a method for regioselective functionalization of indoles (Scheme 1) [2, 20]. Otha and co-workers reported a palladium catalyzed highly selective C3-arylation of *N*-tosyl indole using 2-chloropyrazine [21]. Sames and Lamaire *et al.* developed a Heck-type cross coupling of indole and 4-bromo-3-nitroanisole using palladium acetate and triphenyl phosphine catalytic system for the C3-arylation [22]. Recently, Bellina and co-workers reported a palladium mediated ligand free direct C3- arylation of free (NH)-indoles with aromatic bromides [23]. Gaunt and co-workers demonstrated a Cu catalyzed direct C3-arylation of indoles using aryliodonium salts at room temperature employing the catalytic system $Cu(OTf)_2$/dtbpy [24]. Recently, KO*t*Bu mediated metal free approaches for the synthesis of C3-aryl indoles were developed by Kumar *et al* and Lu *et al* independently by the reaction of NH-free indoles and aryl halides in DMSO (Scheme 1) [25]. Oxindoles were also used to synthesize 3-indoles. Treatment of 3-oxindoles with $POCl_3$ followed by hydrogenation on Pd/C and triethylamine provided the corresponding 3-indoles (Scheme 1) [26]. Kayaki et al. reported an example of the synthesis of a 3-indole derivative from the corresponding 3-oxindole by deoxygenative hydrogenation using pincer-Ru complexes (Scheme 1) [27]. Further, a reductive strategy for the synthesis of 3-indoles from the corresponding 3-substituted-3-hydroxy oxindoles was reported using boranes [28].

Although a number of synthetic methods are available to access 3-substituted indoles, given the importance of the C3-functionalized indoles, the development of a rapid and scalable method with high flexibility in substitution pattern is desirable. Recently, we have reported the synthesis of 2-substituted and 2,3-disubstituted indole derivatives using Grignard addition via dehydrative aromatization involving indolinium ion intermediates (Scheme 1) [29]. We envisioned that instead of Grignard reagent, addition of a hydride nucleophilic source to C3-substituted oxindoles would lead to 3-substituted indoles via the formation of indolinium ion intermediate using aromatization as the driving force (Scheme 1). This methodology will allow an easy access to 3-functionalized indoles from easily synthesizable oxindole starting materials with wide substrate scope.

In order to examine the feasibility of our proposed work, a variety of *N*-protected 3-substituted 2-oxindoles were prepared from *N*-protected isatins (see Scheme S1, Supporting Information, S.I.). The addition of alkyl or aryl Grignard reagents to *N*-substituted isatins **1** followed by $SnCl_2$ mediated reductive deoxygenation of intermediate 3-alkyl/aryl-3-hydroxy oxindole **2** afforded the corresponding oxindoles **3a-i** in good yields (Scheme 2, a) [29, 30]. C3-allyl oxindole precursors **5a-b** were synthesized by allyl indium addition to isatin **1** followed by subsequent reductive deoxygenation of the intermediate **4** (Scheme 2, b).

With the required 3-oxindole precursors in hand, a systematic study was necessary to conduct for the development of the reaction to obtain 3-indole derivatives. Since it is well known that boron and aluminium based reagents are generally used for the reduction of amides via hydride transfer, we began our optimization studies by using $LiAlH_4$, the most commonly used reagent for reduction of amides to amines [31]. Previously, Nishino and co-workers used $LiAlH_4$ for the synthesis of a 3-indole derivative from 3-oxindole [32]. To our delight, when the reaction was performed in the presence of 2 equiv. of $LiAlH_4$ in THF at room temperature for 4 h, the desired product **6a** was obtained in acceptable yield (Table 1, entry 1). However, the yield of the reaction decreased by using 4 equiv. of $LiAlH_4$, keeping other reaction parameters fixed (entry 2). The outcome of the reaction did not alter upon increase of reaction time or

Table 1. Optimization of the reaction[a]



3a 6a

Entry	Hydride source (equiv.)	Solvent	T (° C)	Time (h)	Yield (%); **6a**[b]
1	$LiAlH_4$ (2.0)	THF	Rt	4	65
2	$LiAlH_4$ (4.0)	THF	Rt	4	50
3	$LiAlH_4$ (2.0)	THF	Rt	8	55
4	$LiAlH_4$ (2.0)	THF	70	4	40
5	$LiAlH_4$ (2.0)	THF	0	4	74
6	$LiAlH_4$ (1.5)	THF	0	2	80
7	$LiAlH_4$ (1.5)	THF	0	1	64
8	$LiAlH_4$ (1.0)	THF	0	2	40
9	$LiAlH_4$ (0.5)	THF	0	2	20
10	AlH_3 (1.5)	THF	0	2	trace
11	DIBAL-H (1.5)	THF	0	2	No reaction
12	$Li(O^tBu)_3AlH$ (1.5)	THF	0	2	No reaction
13	BH_3-Me_2S (1.5)	THF	0	2	62
14	$LiAlH_4$ (1.5)	Et_2O	0	2	40
15	$LiAlH_4$ (1.5)	Diglyme	0	2	Trace
16[c]	$LiAlH_4$ (1.5)	THF	0	2	78

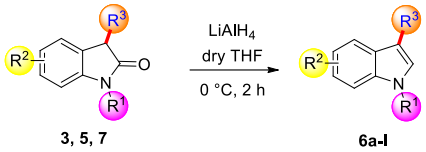
[a]Reaction conditions: **3a** (1.0 equiv, 0.3 mmol). [b]Yield calculated are isolated yields. [c]Preparative scale experiment.

temperature (entry 3 and 4). Yield of **6a** increased by carrying out the reaction at 0 °C (entry 5). **6a** was produced in 80% yield when the reaction was performed using 1.5 equivalent of $LiAlH_4$ at 0 °C for 2 h (entry 6). However, the yield of **6a** dropped to 40%, when the reaction was carried out for 1 h (entry 7). Moreover, use of catalytic amount or 1 equiv. of $LiAlH_4$ (Table 1, entry 8 and 9) was detrimental to the reaction. We next screened different reducing agents under optimized reaction conditions (Table 1, entry 6). Reaction did not proceed with AlH_3, DIBAL-H, $Li(O^tBu)_3AlH$ as the hydride nucleophilic source (Table 1, entry 10-12). However, in the presence of BH_3-Me_2S, **6a** was obtained in 62% yield (Table 1, entry 13). Further optimization studies were then carried out in different solvents generally used for $LiAlH_4$. The yield of **6a** was found to be decreased considerably in diethyl ether and diglyme instead of THF (entry 14-15). It is worth noting that the reaction was scaled (1.0 g of **3a**) without loss of yield under the optimized conditions (entry 16).

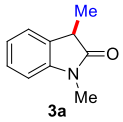
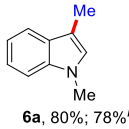
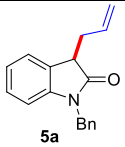
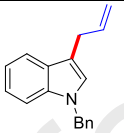
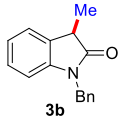
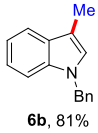
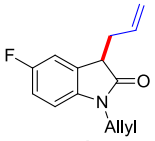
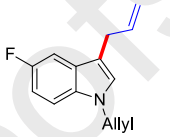
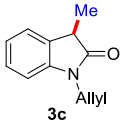
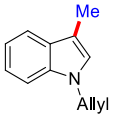
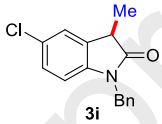
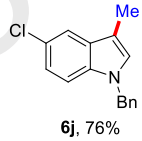
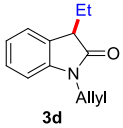
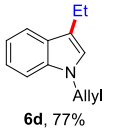
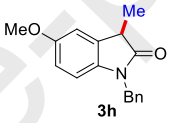
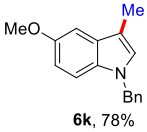
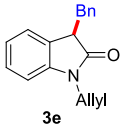
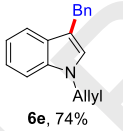
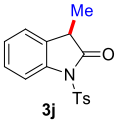
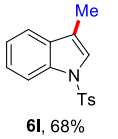
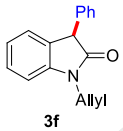
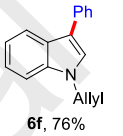
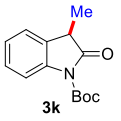
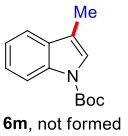
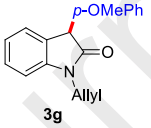
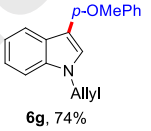
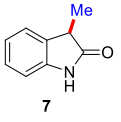
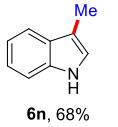
With the optimal reaction conditions (Table 1, entry 6), the scope and generality of this methodology was subsequently explored with respect to substitution in the C3-position as well as aromatic ring of the oxindole moiety. The oxindoles containing different alkyl and aryl C3-substituents such as methyl, ethyl, allyl, benzyl, phenyl and 4-methoxy phenyl were converted to the corresponding 3-substituted indoles (Table 2, **6a-h**) in excellent yields. Oxindoles containing both electron donating and withdrawing substituents in the aromatic ring provided the corresponding C3-indoles in excellent yields (Table 2, **6i-k**). The oxindoles bearing different halo substituents were effectively converted to the corresponding indoles (**6i** and **6j**) in good yields. These halo indoles can be used as precursors for further synthetic transformations by cross-coupling reactions. Electron donating methoxy and electron withdrawing fluoro functional groups are well tolerated under the reaction conditions to furnish the corresponding indoles **6k** and **6i** in good yields (Table 2). The *N*-Ts protected 3-indole derivative **6l** was obtained in 72% yield, whereas reaction with *N*-Boc protected 3-oxindole **3k** failed to provide the corresponding 3-indole **6m** (Table 2).

It is intriguing to find that the NH-free oxindole precursor **7** provided the product 3-methyl indole **6n** in good yield. The reaction was performed in gram scales (see Scheme S6 and S7, Supporting Information, S.I.) successfully affording 3-substituted indoles **6a** and **6i** in good yields (78% and 70% respectively).

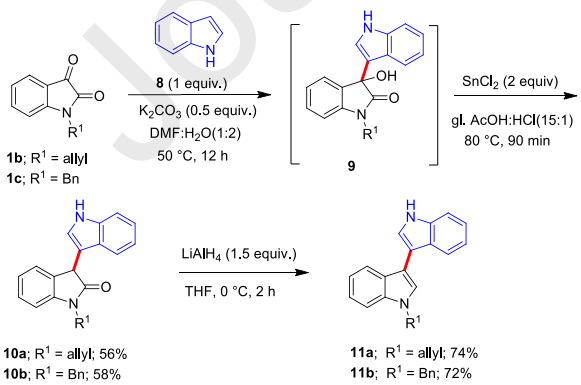
Table 2. Synthesis of 3-substituted indoles[a].



3, 5, 7 → 6a-l

entry	Substrate	Product	entry	Substrate	Product
1	 **3a**	 **6a**, 80%; 78%[b]	8	 **5a**	 **6h**, 81%
2	 **3b**	 **6b**, 81%	9	 **5b**	 **6i**, 78%; 70%[b]
3	 **3c**	 **6c**, 84%	10	 **3i**	 **6j**, 76%
4	 **3d**	 **6d**, 77%	11	 **3h**	 **6k**, 78%
5	 **3e**	 **6e**, 74%	12	 **3j**	 **6l**, 68%
6	 **3f**	 **6f**, 76%	13	 **3k**	 **6m**, not formed
7	 **3g**	 **6g**, 74%	14	 **7**	 **6n**, 68%

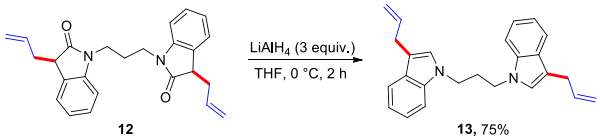
[a]The reactions were performed using 3-oxindole (0.3 mmol, 1 equiv.) with $LiAlH_4$ (1.5 equiv.) in THF (4 mL) for 2 h at 0 °C. [b]Yields refer to the gram scale experiment.



Scheme 3. Synthesis of bis-indoles.

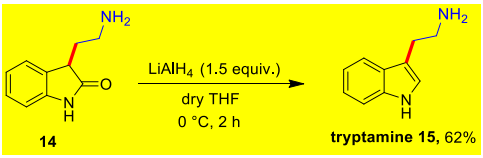
Next the method was used for the synthesis of bis-indoles [33] **11** (Scheme 3) from C3-indolyl oxindoles **10**. Base mediated addition of indole **8** to isatin **1** [34] followed by subsequent $SnCl_2$ mediated reductive deoxygenation of intermediate **9** afforded oxindole derivatives **10a-b** (Scheme 3) [29]. To our delight, reaction of **10a-b** with $LiAlH_4$ under the standard conditions produced the corresponding 3,3´-bisindoles **11a-b** in 74% and 72% yields, respectively (Scheme 3).

Furthermore, the synthesis of a dimeric indole derivative **13** was achieved using the developed protocol. Reaction of dimeric oxindole **12**, prepared using our developed method [29], with $LiAlH_4$ provided **13** in 75% yield (Scheme 4; Scheme S8, S.I.).



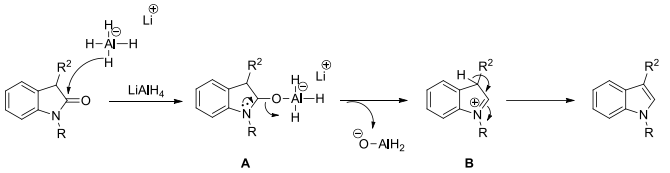
Scheme 4. Synthesis of a dimeric 3-substituted indole derivative.

the synthesis of naturally occurring amino acid tryptamine [8]. Reaction of oxindole **14** with $LiAlH_4$ provided tryptamine **15** in 62% isolated yield (Scheme 5).



Scheme 5. Synthesis of tryptamine.

We presume that the addition of $LiAlH_4$ to oxindoles generates the intermediate **A** via hydride transfer to the amide carbonyl of the oxindole (Scheme 6). Elimination of $\bar{O}AlH_2$ leads to the formation of indolinium ion intermediate **B** [29, 35]. Subsequent aromatization provides the desired indole derivatives (Scheme 6). As aromatization is the driving force, C3-hydrogen elimination is faster than another hydride transfer from $LiAlH_4$ to the indolinium ion intermediate **B**.



Scheme 6. Plausible mechanism for the formation of 3-indoles via hydride transfer.

In summary, we have developed a general protocol for the synthesis of 3-substituted indoles using an optimized amount of $LiAlH_4$. The synthetic pathway proceeds via hydride transfer to the oxindole moiety involving indolinium ion intermediate followed by aromatization. Various 3-functionalized alkyl and aryl indoles were obtained in excellent yields. The 3,3′-bis-indoles were also obtained in high yields using this method. The synthesis of a dimeric indole derivative further highlights the efficiency of the developed protocol. The method described herein is mild, simple and efficient, providing a convenient synthetic access to a wide variety of 3-substituted indoles.

Declaration of competing interests

The authors declare no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Supplementary Material

^{1}H NMR and ^{13}C NMR data and spectra and HRMS data of the products are available. Supplementary data to this article can be found online at https://doi.org/

References

1. For recent reviews, see: (a) Kawasaki, T.; Higuchi, K. *Nat. Prod. Rep*. **2005**, *22*, 761;
   (b) Kochanowska-Karamyan, A. J. *Chem. Rev*. **2010**, *110*, 4489;
   (c) Inman, M.; Moody, C. J. *Chem. Sci*. **2013**, *4*, 29 and references therein.
2. Robert, F. M.; Wink, M. *Alkaloids: Biochemistry, Ecology, and Medicinal Applications*; Plenum: London, **1998**.
3. von Nussbaum, F. *Angew. Chem. Int. Ed*. **2003**, *42*, 3068.
4. Pindur, U.; Lemster, T. *Curr. Med. Chem.* **2001**, *8*, 1681.
5. Sundberg, R. J. *Indole*; Acedemic Press: New York, **1996**, 1.
6. Radwanski, R. E.; Last, L. R. *Plant Cell* **1995**, *7*, 921.
7. Jones, R. S. *Progress Neurobiol.* **1982**, *19*, 117.
8. Della, G.; Djura, P.; Sargent, M. V. *J. Chem. Soc. Perkin Trans.* **1981**, *1*, 1679.
9. Fusetani, N.; Sugawara, T.; Matsunga, S. *J. Org. Chem.* **1991**, *56*, 4971.
10. Guerriero, A.; Ambrosio, M. D.; Pietra, F.; Debitus, C.; Ribes, O. *J. Nat. Prod.* **1993,** *56*, 1962.
11. Bobzin, C. S.; Faulkner, D. J. *J. Org. Chem*. **1991**, *56*, 4403-4407.
12. Bewely, A. C.; Faulkner, D. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 2162.
13. (a) B. Robinson, *The Fischer Indole Synthesis*; Wiley, **1982**;
    (b) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc*. **1998**, *120*, 6621;
    (c) Alex, K.; Tillack, A.; Schwarz, N.; Beller, M. *Angew. Chem. Int. Ed*. **2008**, *47*, 2304;
    (d) Haag, B. A.; Zhang, Z. -G.; Li, J. -S.; Knöchel, P. *Angew. Chem. Int. Ed*. **2010**, *49*, 9513.
14. (a) Yadav, J. S.; Reddy, B. V. S.; Reddy, P. M.; Srinivas, C.*Tetrahedron Lett*., **2002**, *43*, 5185;
    (b) Yadav, J. S.; Reddy B. V. S.; Swamy, T. *Tetrahedron Lett*. **2003**, *44*, 9121;
    (c) Mukherjee, D.; Sarkar, S. K.; Chowdhury, U. S.; Taneja, S. C. *Tetrahedron Lett*. **2007**, *48*, 663;
    (d) Smith, M. B.; Guo, L. C.; Okeyo, S.; Stenzel, J.; Yanella, J.; LaChpelle, E. *Org. Lett*. **2002**, *4*, 2321;
    (e) Bartoli, G.; Bosco, M.; Carlone, A.; Pesciaioli, F.; Sambri, L.; Melchiorre, P. *Org. Lett*. **2007**, *9*, 1403.
15. Ackermann, L.; Born, R. *Tetrahedron Lett*., **2004**, *45*, 9541.
16. Yaragorla, S.; Kumar, S. G. *Indian Journal of Chemistry.* **2015**, *54B*, 240.
17. Palmeiri, A.; Petrini, M.; Shaikh, R. R. *Org. Biomol. Chem.* **2010**, *8*, 1259.
18. Singh, V. K.; Dubey, R.; Upadhyay, A.; Sharma, L. K.; Singh, R. K. P. *Tetrahedron Lett*. **2017**, *58*, 4227.
19. Cacchi, S.; Fabrizi, G. *Chem. Rev*. **2006**, *105*, 2873.
20. Akita, Y.; Itagaki, Y.; Takizawa, S.; Ohta, A. *Chem. Pharm. Bull*. **1989**, *37*, 1477.
21. David, E.; Lejeune, J.; Pellet-Rostaing, S.; Schulz, J.; Lemaire, M.; Chauvin, J.; Deronzier, A.; *Tetrahedron Lett*. **2008**, *49*, 1860.
22. Bellina, F.; Benelli, F.; Rossi, R. *J. Org. Chem*. **2008**, *73*, 5529.
23. Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc*. **2008**, *130*, 8172.
24. (a) Kumar, S.; Rathore, V.; Verma, A.; Prasad, Ch. D.; Kumar, A.; Yadav, A.; Jana, S.; Sattar, M.; Meenakshi; Kumar, S. *Org. Lett.* **2015**, *17*, 82;
    (b) Chen, J.; Wu, J. *Angew. Chem. Int. Ed*. **2017**, *56*, 3951.
26. Kubo. A.; Nakai, T. *Synthesis* **1980**, 365.
27. Ogata, O.; Nara, H.; Matsumura, K.; Kayaki, Y. *Org Lett*. **2019**, 9954.
28. Wierenga, W.; Griffin, J.; Warpehoski, M. A. *Tetrahedron Lett*. **1983**, *24*, 2437.
29. Mandal, T.; Chakraborti, G.; Karmakar, S.; Dash, J. *Org. Lett*. **2018**, *20*, 4759.
30. Huang, A.; Kodanko, J. J.; Overman, L. E. *J. Am. Chem. Soc*. **2004**, *126*, 14043.
31. (a) de. Mayo, P.; Rigby, W. *Nature*. **1950**, *166*, 1075;
    (b) Morrison, A. L.; Long, R. F.; Konigstein, M. *J. Chem. Soc.* **1951**, 952;
    (c) Micovic, V.; Mihailovic, M. *J. Org. Chem.* **1953**, *18*, 1190
32. Kikue, N.; Takahasi, T.; Nishino, H. *Heterocycles* **2015**, *90*, 540.
33. (a) Berens, U.; Brown, J. M.; Long, J.; Selke, R. *Tetrahedron Asymmetry* **1996**, *7*, 285;
    (b) Li, Y.; Wang, W. –H.; Yang, S. –D.; Li, B. –J.; Feng, C.; Shi, Z. –J. *Chem. Commun*. **2010**, *46*, 4553.
34. Zhang, F. –L.; Zhu, X.; Chiba, S. *Org. Lett.* **2015**, *17*, 3138.
35. (a) Dhara, K.; Mandal, T.; Das, J.; Dash, J. *Angew. Chem. Int. Ed.* **2015**, *54*, 15831;
    (b) Mandal, T.; Chakraborti, G.; Maiti, S.; Dash, J. *Org. Lett*. **2019**, *21*, 8044.

Highlight

- Practical and scalable synthetic route to 3-indoles
- Partial reduction-aromatization of oxindoles to 3-indoles using $LiAlH_4$
- The reaction proceeds via an indolinium ion intermediate
- Synthesis of a diverse class of 3-indoles and bis-indoles
- A quick access to tryptamine

Graphical Abstract

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Reductive aromatization of oxindoles to 3-substituted indoles

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Tirtha Mandal, Gargi Chakraborti and Jyotirmayee Dash*