Tetrahedron Letters xxx (xxxx) xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

CuI-catalyzed highly regioselective C—H functionalization of indoles using indole-3-tosylhydrazones as carbene precursor: An efficient synthesis of 3,3-bis(indolyl)methane derivatives

Priya Kamboj [a], Sunil Dutt [a], Sourav Chakroborty [b], Vikas Tyagi [a,*]

[a] School of Chemistry and Biochemistry, Thapar Institute of Engineering and Technology, Patiala 147004, Punjab, India
[b] Institute of Science and Supramolecular Engineering, CNRS, 7006 UMR University of Strasbourg, 8 rue Gaspard Monge, 67000 Strasbourg, France

ARTICLE INFO

Article history:
Received 19 July 2019
Revised 11 September 2019
Accepted 16 September 2019
Available online xxxx

Keywords:
Bis indoles
N-tosylhydrazone
Copper-catalyst
Regioselective
Carbene insertion

ABSTRACT

Herein, we have developed a novel approach for synthesizing symmetrical and unsymmetrical 3,3-bis (indolyl)methane derivatives via CuI-catalyzed C—H functionalization of indole using indole-3-tosylhydrazones as carbene precursor. This procedure works well with different substitutions such as NO_2, Br, CH_3 and OMe on indole or indole-3-tosylhydrazones and features high regioselectivity for C-3 functionalization over the C-1 and N-1 positions. Further, we have also revealed the feasibility of this protocol in a one-pot fashion starting from indole-3-carboxyaldehyde.

Introduction

Bis-indoles belong to a structurally fascinating and imperative class of heterocycles as they are broadly found in a number of pharmacologically and biologically important natural as well as synthetic compounds (Fig. 1) [1]. Moreover, 3,3-bis(indolyl) methanes (BIM) derivatives possesses two indole units linked by a methylene bridge exhibited remarkable biological activities such as anti-inflammatory, antihyperglycemic, antiviral, antibacterial, anticancer etc [2]. Therefore, the effective preparation of 3,3-bis (indolyl)methane derivatives have attracted great attention in the chemical community over the past years [3].

In general, the 3,3-bis(indolyl)methane can be prepared by reaction of indoles with various aromatic or aliphatic aldehydes or ketones in the presence of Lewis acids or Bronsted acids [4]. These traditional methods have a number of disadvantages e.g., longer reaction time, requirement of more than stoichiometric amount of reagents and tedious aqueous work-up. The deactivation of Lewis acids or sometimes possible decomposition by nitrogen containing reactants may also create problems.

In this regard, numerous alternative methods have been developed to overcome aforementioned limitations to some extent [5]. However, the synthesis of 3,3-bis(indolyl)methane having methylene bridge is quite challenging and only a few methods were reported [1g]. In this context, Deb and his co-workers have been reported a microwave assisted Ru(III)/TBHP-mediated reaction of indoles with tetramethylurea to prepare bis(indolyl)methanes (Scheme 1a) [6]. Afterwards, Loh *et. al.* has been reported the synthesis of 3,3-bis(indolyl)methanes catalyzed by Mg-Al mixed oxides supported iridium catalyst (Scheme 1b) [7]. But, these methods also have certain drawbacks such as only applicable to produce symmetrical bis(indolyl)methanes consisting methylene bridge efficiently. So, an efficient method is highly desirable to prepare both symmetrical and unsymmetrical 3,3-bis(indolyl) methane derivatives.

On the other hand, the functionalization of indole ring using transition-metal catalysts and substituted diazo compounds as carbene precursor have widely been explored [8]. For example, Zhou et al. used copper and palladium based complexes to catalyze the selective C—H functionalization of indoles with diazo compounds [9]. Very recently, Fasan's group reported a biocatalytic strategy for enabling the direct C3-functionalization of unprotected indoles [10]. The CuI-catalyzed 3-alkylation of indoles using *N*-tosylhydrazones as carbene precursor was reported by Yang's group [11]. Despite the usefulness of carbene insertion in C—H functionalization of indole, it suffers from competing reactions at C-2 and N-1 positions of the indole ring [12]. In order to develop an efficient method for the synthesis of 3,3-bis(indolyl)methanes

* Corresponding author.
E-mail address: vikas.tyagi@thapar.edu (V. Tyagi).

https://doi.org/10.1016/j.tetlet.2019.151162
0040-4039/

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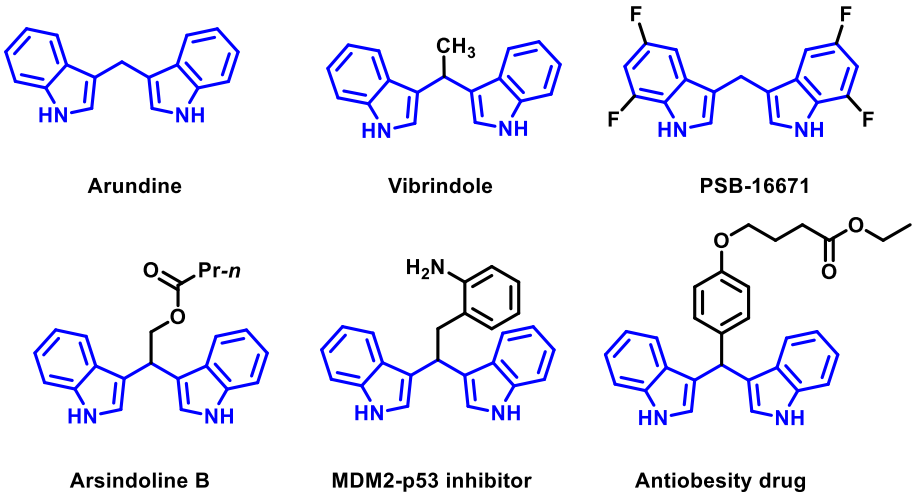
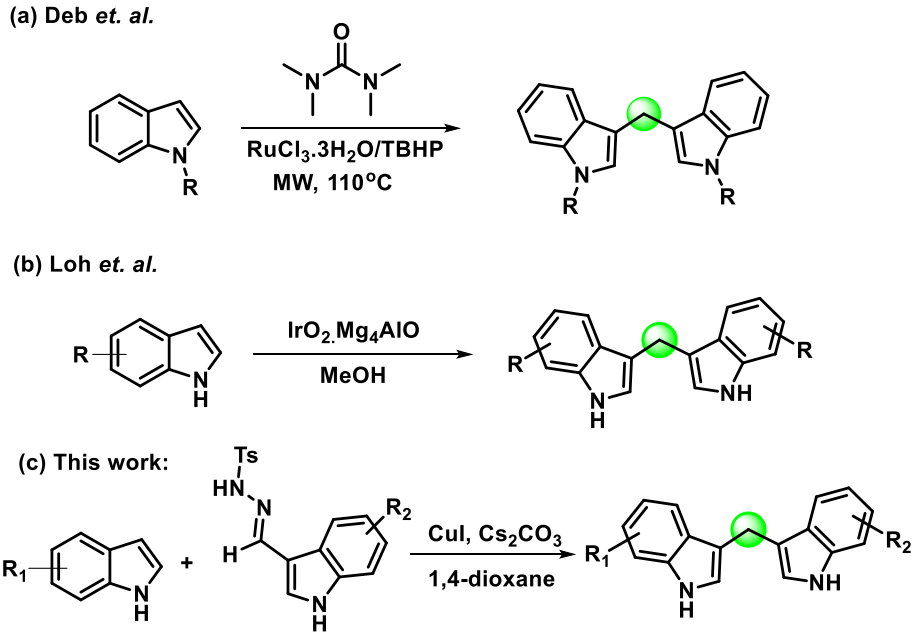


Fig. 1. Representative structures of biologically active 3,3-bis(indolyl)methane containing natural or synthetic compounds.



Scheme 1. Methods for the synthesis 3,3-bis(indolyl)methane consisting methylene bridge.

having methylene bridge, herein, we have designed a copper catalyzed regioselective C—H functionalization of indole using indole-3-tosylhydrazone as carbene precursor (Scheme 1c).

Results and discussion

We have started our investigation by considering the reaction of indole **(1a)** with tosylhydrazone **(2a)** as a model reaction for the optimization of the reaction conditions and all the results were summarized in Table 1. First, we have tested CuI as catalyst with K_2CO_3 as a base in 1,4-dioxane and obtained the product **(3a)** in 49% yield, whereas only trace amount of product (3a) was observed in the presence of $Pd(OAc)_2$ (entry 1–2, Table 1). When, we replaced K_2CO_3 with KO*t*Bu as a base in the presence of $Pd(OAc)_2$ as catalyst, there was no improvement in the formation of **(3a)** (entry 3, Table 1). Next, we screened various bases such as NaOH, Cs_2CO_3, KO*t*Bu, LiOtBu, DBU and Et_3N with CuI as catalyst to increase the yield of model reaction (entry 4–9, Table 1) and Cs_2CO_3 was found the most effective one (entry 5, Table 1). Also, 2.0 equiv. of Cs_2CO_3 was essential to obtain maximum conversion (entry 10–11, Table 1). Interestingly, replacement of CuI with CuBr, CuCl, $CuSO_4$ and $Cu(OAc)_2$ provided **(3a)** either in inferior yield or only in trace amount (entry 12–15, Table 1).

Next, the use of different solvents in the combination of CuI as catalyst and Cs_2CO_3 as base, did not showed any improvement in the yield of **(3a)** (entry 16–21, Table 1). It was also observed that there was no product formation in the absence of either CuI or base (entry 22–23, Table 1). Further optimization revealed that 10 mol% of CuI was essential to get the maximum conversion in this reaction (entry 24–25, Table 1).

After having the optimal reaction conditions (entry 5, Table 1) for the synthesis of bisindoles **(3a)**, the effect of different substitutions on indole **(1)** and tosylhydrazone **(2)** was tested and all the results were summarized in Table 2. Initially, we have tested the scope of substitution for the synthesis of symmetrical bisindoles

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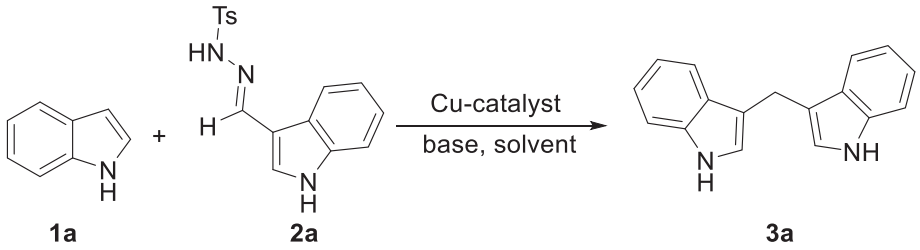
Table 1
Optimization of the reaction conditions for the regioselective C—H functionalization of indole.[a]



entry	catalyst	base	solvent	yield %[b]
1	CuI	K_2CO_3	1,4-dioxane	49
2	$Pd(OAc)_2$	K_2CO_3	1,4-dioxane	trace
3	$Pd(OAc)_2$	KO^{t}Bu	1,4-dioxane	trace
4	CuI	NaOH	1,4-dioxane	27
5	**CuI**	**Cs_2CO_3**	**1,4-dioxane**	**59**
6	CuI	KO^{t}Bu	1,4-dioxane	42
7	CuI	LiO^{t}Bu	1,4-dioxane	34
8	CuI	DBU	1,4-dioxane	trace
9	CuI	Et_3N	1,4-dioxane	13
10	CuI	Cs_2CO_3	1,4-dioxane	44[c]
11	CuI	Cs_2CO_3	1,4-dioxane	55[d]
12	CuBr	Cs_2CO_3	1,4-dioxane	41
13	CuCl	Cs_2CO_3	1,4-dioxane	20
14	$CuSO_4$	Cs_2CO_3	1,4-dioxane	trace
15	$Cu(OAc)_2$	Cs_2CO_3	1,4-dioxane	trace
16	CuI	Cs_2CO_3	toluene	51
17	CuI	Cs_2CO_3	DMF	49
18	CuI	Cs_2CO_3	THF	20
19	CuI	Cs_2CO_3	DMSO	trace
20	CuI	Cs_2CO_3	DMA	51
21	CuI	Cs_2CO_3	CH_3CN	26
22	–	Cs_2CO_3	1,4-dioxane	0[e]
23	CuI	–	1,4-dioxane	0[e]
24	CuI	Cs_2CO_3	1,4-dioxane	32[f]
25	CuI	Cs_2CO_3	1,4-dioxane	61[g]

[a] Reaction conditions: All reactions were performed in a 10 mL sealed tube using indole **1a** (1.2 equiv., 0.96 mmol), indole-3-tosylhydrazone (1.0 equiv., 0.64 mmol), catalyst (10 mol %) and base (2.0 equiv. 1.27 mmol), solvent 2 mL at 110 °C for 15–18 h at conventional heating,
[b] isolated yield,
[c] used 1.0 equiv. of base,
[d] used 3.0 equiv. of base
[e] no reaction,
[f] used 5 mol% of catalyst,
[g] used 20 mol% of catalyst.

(entry 1–4, Table 2) and we obtained good yields of corresponding symmetrical bisindoles in case of 5-Br, and 2-CH_3 substitutions (entry 2–3, Table 2). In contrast, 5-nitro substitution gave the inferior yield of the product (entry 4, Table 2) and it might be due to the instability of the product. Next, we have seen the effect of electron withdrawing and donating group for the synthesis of unsymmetrical indoles. To our delight, many substitutions e.g. -CH_3, -OCH_3, and -Br irrespective of the positions on the phenyl ring of indole-3-tosylhydrazone were found compatible with good yields of the resultant products (entry 5–8, Table 2), however, the yield of corresponding product was slightly higher in the case of 5-OMe substitution (entry 6, Table 2). Further, when we had mild electron withdrawing group (-Br) on **(1)** and electron donating group (-CH_3 or -OMe) on **(2)**, reaction gave 58–69% yields (entry 9–11, Table 2). Whereas, 5-Br and 4-Br substitutions on **(1)** and **(2),** respectively, were furnished the corresponding product in 56% yield (entry 12, Table 2). We got the product in 43% yield, when started the reaction of 5-NO_2-indole with indole-3-tosylhydrazone containing 5-Br substitution (entry 13, Table 2). Further, no reaction was observed in the case of 3-Me substitution at tosylhydrazone **(2)**, which proves the regioselectivity of this transformation. Besides, we have observed the formation of a complex mixture of indole-3-carboxyaldehyde, sulfone and other unidentified products in some reactions due to the decomposition of tosylhydrazones via its self-reaction in the presence of Cs_2CO_3 and CuI [13], as a result reactions gave moderate yield of the desired products.

We continued our investigation to find the role of substitution on the N-1 position of indole as well as indole based tosylhydrazone. When, we used *N*-methyl indole **(4)** with indole-3-tosylhydrazone **(2a)**, no product formation was observed (Scheme 2a). Whereas, in the reaction of unsubstituted indole **(1a)** with *N*-methyl-indole based tosylhydrazone **(5)** only undesired product **(6)** was isolated (Scheme 2b). These results proves the importance of substitution on N-1 position in this reaction which was also observed previously by Shi et al. [5b].

In order to show the scalability of this methodology, we have started a reaction of indole **(1a)** (0.56 g, 4.78 mmol) with tosylhydrazone **(2a)** (1 g, 3.19 mmol) under the optimized reaction conditions (Scheme 3). Gratifyingly, we obtained the isolated product **(3a)** in 52% yield (0.41 g) from this reaction which demonstrated the synthetic utility of this transformation.

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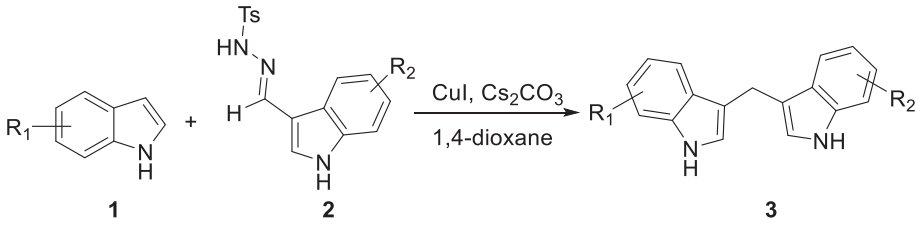
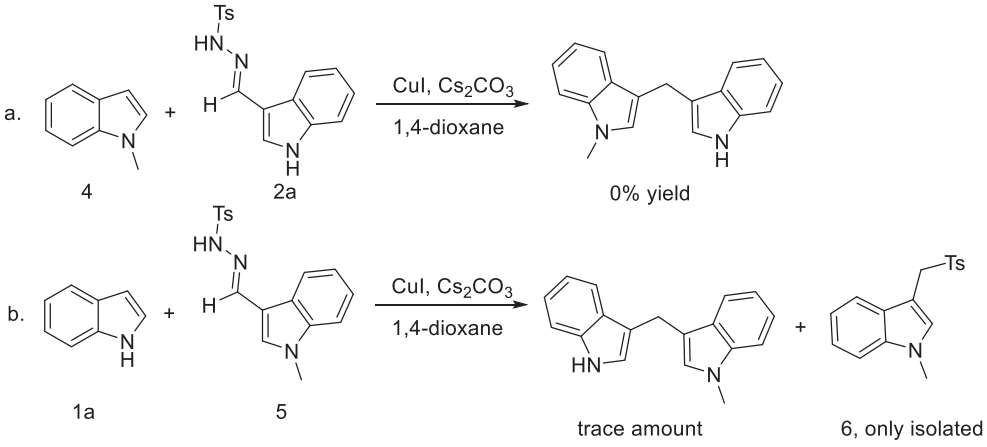
Table 2
Substrate scope for the regioselective C—H functionalization of indole using indole-3-tosylhydrazone.[a]

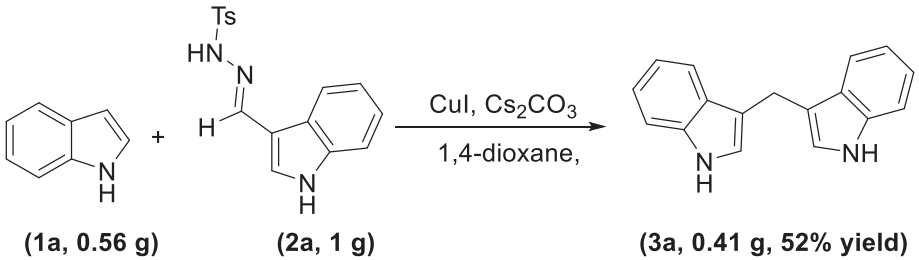


entry	R_1	R_2	product, %yield
1	H	H	3a, 59
2	5-Br	5-Br	3b, 63
3	2-CH_3	2-CH_3	3c, 69
4	5-NO_2	5-NO_2	3d, 39
5	H	2-CH_3	3e, 61
6	H	5-OMe	3f, 71
7	H	5-Br	3g, 63
8	H	4-Br	3h, 67
9	5-Br	2-CH_3	3i, 58
10	4-Br	2-CH_3	3j, 65
11	5-Br	5-OMe	3k, 69
12	5-Br	4-Br	3l, 56
13	5-NO_2	5-Br	3m, 43
14	H	3-CH_3	3n, 0[b]

[a] Reaction conditions: All reactions were performed in a 10 mL sealed tube using indole **1a** (1.2 equiv., 0.96 mmol), indole-3-tosylhydrazone (1.0 equiv., 0.64 mmol), CuI (10 mol %) and Cs_2CO_3 (2.0 equiv., 1.27 mmol) in 1,4-dioxane (2 mL) as solvent at 110 °C for overnight,
[b] no reaction.



Scheme 2. Control experiments to examine the role of substitutions on N-1 position.



Scheme 3. Gram-scale reaction to synthesize the bisindole (**3a**).

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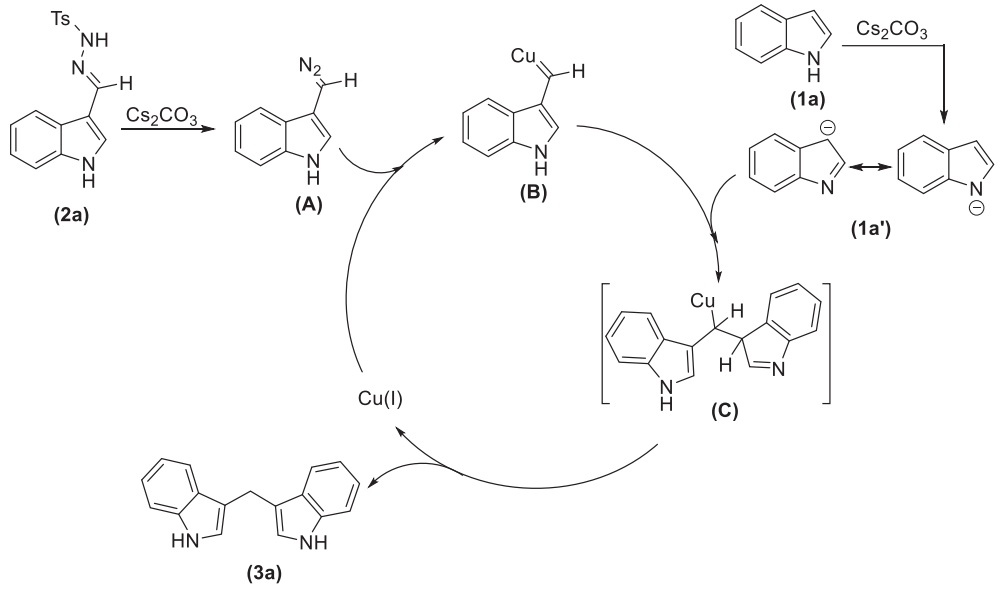
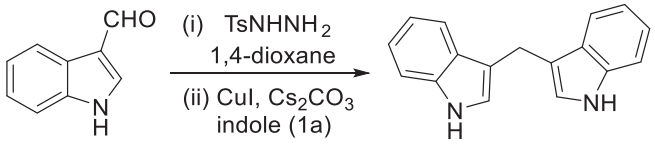


Scheme 4. Plausible mechanism for the synthesis of bisindoles.



Scheme 5. Synthesis of bisindole **(3a)** in a one-pot fashion.

Further, we have proposed a possible mechanism for the CuI-catalyzed regioselective formation of bisindoles **(3a)** based on relevant reports (Scheme 4) [13,8g,9b]. Initially, diazo **(A)** as the key intermediate was formed via base (Cs_2CO_3) mediated decomposition of indole-3-tosylhydrazone **(2a)**. Next, the diazo intermediate reacts with CuI to generate Cu(I) carbene complex **(B)**, which reacted with deprotonated indole **(1a′)** [13] regioselectively at the C-3 position to form a metal associated intermediate **(C).** Then, proton migration from C-3 position of indole to the α–position taken place to provide the bisindole product **(3a)**.

Finally, to test the feasibility of the methodology in a one-pot fashion without isolating the indole-3-tosylhydrazine precursor (Scheme 5). We have started a reaction using indole-3-carboxyaldehyde (3.44 mmol) and tosylhydrazine (4.13 mmol) in 1, 4-dioxane as a solvent at 60 °C. After the total consumption of the indole-3-carboxyaldehyde, indole (2.39 mmol), CuI (10 mol%), and Cs_2CO_3 (3.19 mmol) were added and stirred the resulting mixture at 110°C for overnight. The yield of purified bisindole product **(3a)** was found 53%, which was slightly lower than the step-wise procedure.

Conclusions

In summary, we have developed a novel CuI-catalyzed regioselective C—H functionalization of indole using indole-3-tosylhydrazons as carbene precursor for synthesizing 3,3-bis(indolyl) methanes derivatives. Moreover, this methodology can be used for the synthesis of symmetrical and unsymmetrical 3,3-bis (indolyl)methanes in moderate to good yields. A number of substitutions such as NO_2, Br, CH_3 and OMe on indole or indole-3-tosylhydrazones were tolerated well in this protocol. Further, we demonstrated the feasibility of this protocol in a one-pot fashion starting from indole-3-carboxyaldehyde which gave result very close to step-wise protocol. The biological screening of the synthesized compound is under progress in our lab and will be reported in due course.

Acknowledgement

We acknowledge the financial support from Department of Science and Technology, India (DST/INSPIRE/04/2017/000095).

Appendix A. Supplementary data

All the experimental procedure and characterization data and copies of NMR spectra to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151162.

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Please cite this article as: P. Kamboj, S. Dutt, S. Chakroborty et al., CuI-catalyzed highly regioselective C—H functionalization of indoles using indole-3-tosylhydrazones as carbene precursor: An efficient synthesis of 3,3-bis(indolyl)methane derivatives, Tetrahedron Letters, https://doi.org/10.1016/j.tetlet.2019.151162