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Synthesis of Chiral Tryptamines via a Regioselective Indole Alkylation

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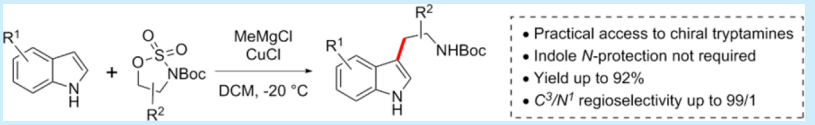
Supporting Information



ABSTRACT: A practical synthesis of chiral tryptamines from simple, unprotected indoles has been developed. Indole nucleophiles prepared with MeMgCl in the presence of CuCl reacted with chiral cyclic sulfamidates almost exclusively at the C^3-position of indole to form a variety of α- and/or β-substituted chiral tryptamines in good yield with excellent regioselectivity. The utility of this simple alkylation process has been demonstrated with the practical synthesis of two biologically active targets, cipargamin and TIK-301, which were completed in three steps, starting from the corresponding indole starting materials.

Chiral tryptamines are frequently encountered in pharmacology, because of their significant biological activities in the central nervous system.[1] In addition, the chiral tryptamine moiety serves as the synthetic precursor of many medicinally important indole alkaloids and is found in numerous biologically active natural products and pharmaceuticals (see Figure 1).[2]

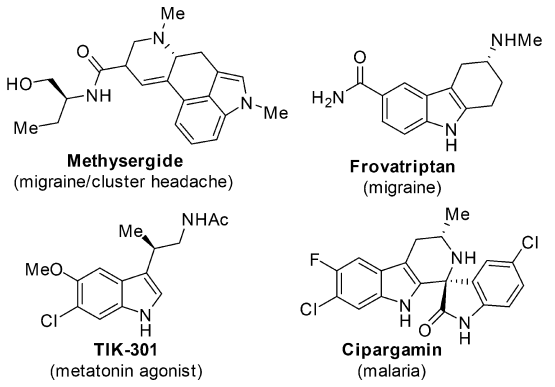
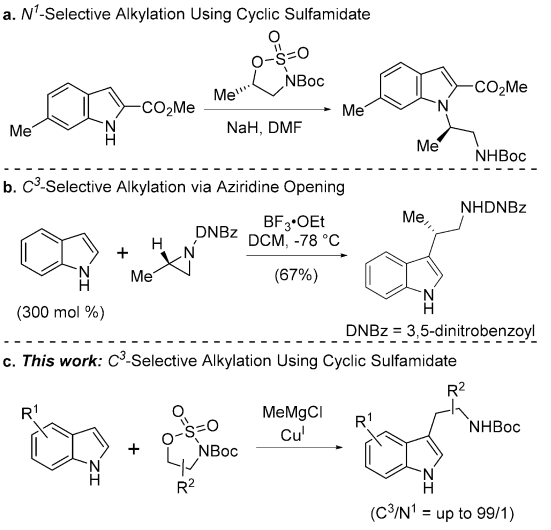


Figure 1. Chiral tryptamine-containing pharmaceuticals.

In particular, stereocontrolled synthesis of tetrahydro-β-carboline-containing compounds such as cipargamin often relies on the diastereoselective Pictet−Spengler reaction, which, in turn, requires enantiomerically pure tryptamines as starting material.[3] The latter is typically prepared in a nonstereoselective manner via a multistep sequence involving hazardous nitroalkane reagents or prepared by Larock indolization via a three-step sequence requiring the use of palladium and additional silyl deprotection.[4] Therefore, the development of a simple regioselective alkylation approach that involves readily available nonprotected indoles as nucleophiles and chiral amine-derived electrophiles, such as chiral aziridines and cyclic sulfamidates, would provide convenient access to these valuable chiral scaffolds. Indeed, the C^3-selective indole alkylation had been the subject of extensive studies in order to overcome the unwanted alkylation at the C^2 or N^1 positions.[5]

However, there are only limited examples where these approaches were used in a stereocontrolled manner. For instance, it is reported that the use of chiral aziridines or cyclic sulfamidates as reaction partners preferentially provided N^1-alkylation (see Scheme 1a).[6] Aziridine electrophiles have been applied to provide C^3-selective alkylation under Lewis acidic

Scheme 1. Regioselective Indole Alkylation



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conditions; however, this method is only applicable to the synthesis of β-substituted tryptamines, because the displacement occurs preferentially at the more-substituted carbon (see Scheme 1b).[7] Here, we report that low-order cuprate of indoles, in combination with chiral cyclic sulfamidates, successfully provide practical access to both α- and β-substituted chiral tryptamines with high regioselectivity (see Scheme 1c).

At the outset, and while avoiding the protective group on the indole, we considered the use of either chiral aziridines or cyclic sulfamidates as the electrophile. It was found that the reaction with the former always led to a mixture of α-and β-substituted tryptamines, while the latter unambiguously reacted to displace the C−O bond.[8] Therefore, we chose the cyclic sulfamidates as the reaction partner for our optimization studies (see Table 1).

Table 1. Optimization of Sulfamidate Alkylation[a]

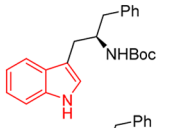
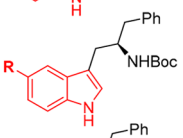
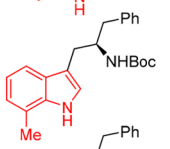
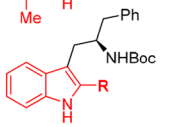
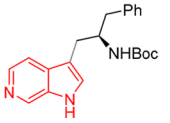
entry	base/additive (temperature)	isolated yield (%)	C^3/N^1[b]
1	MeMgCl/none (−10 °C)	14	31/69
2	MeMgCl/CuCl (−10 °C)	66	95/5
3	MeMgCl/CuBr (−10 °C)	37	95/5
4	MeMgCl/CuI (−10 °C)	26	90/10
5[c]	MeMgCl/CuCl (−10 °C)	38	67/33
6	MeMgCl/$ZnCl_2$ (−10 °C)	38	22/78
7	MeMgCl/$ZnBr_2$ (−10 °C)	28	37/63
8	MeMgBr/CuCl (−10 °C)	26	45/54
9	PhMgCl/CuCl (−10 °C)	66	96/4
10	MeLi/CuCl (−10 °C)	N.D.[d]	11/89
11	MeMgCl/CuCl (−40 °C)	N.D.[d]	42/58
12[e]	MeMgCl/CuCl (−20 °C)	76	97/3
13	MeMgCl/CuCl (−0 °C)	65	95/5

[a]Base (130 mol %) was added to a mixture of **1a** (150 mol %) and additive (130 mol %) in DCM followed by **5a** (100 mol %) in DCM (0.2−0.5 mol/L). [b]Determined by HPLC analysis. [c]A catalytic amount of CuCl (20 mol %) was used. [d]Not determined. [e]The cuprate was prepared at 0 °C, and **5a** was added at −20 °C.

Contrary to the literature precedents, which suggest preferential alkylation at the C^3-position when Grignard reagents were used as a base, our initial attempts were met with low yields and poor site selectivity (see Table 1, entry 1).[5a] Postulating that the softer indole nucleophile would prefer to react as a carbon-centered nucleophile, various additives, including Cu and Zn salts, were surveyed. Interestingly, a mixed halide system such as MeMgCl, in combination with CuBr or CuI, or MeMgBr in combination with CuCl was much less efficient than the chloride-only system (see Table 1, entries 2, 3, 4, and 8).[9] In our hands, other copper salts, such as $CuCl_2$, CuCN, CuTC, or Cu(SCN), were also inferior to CuCl.[10] A catalytic amount of CuCl was not tolerated, resulting in significant decreases in yield and selectivity (see Table 1, entry 5). Notably, a reversal of regioselectivity was observed when zinc halides were used instead of CuCl (see Table 1, entries 6 and 7). The same was true when MeLi was used as base instead of MeMgCl (see Table 1, entry 10), while the use of another Grignard reagent was well-tolerated (see Table 1, entry 9). Finally, we evaluated the effect of reaction temperature, and established that the displacement reaction performed optimally at approximately −20 °C. At below −30 °C, a significant drop in regioselectivity was observed, presumably due to the incomplete cuprate formation (see Table 1, entries 11−13).[11]

With the optimized conditions in hand, the generality of this reaction was examined next, and the results are summarized in Tables 2 and 3. Encouragingly, the Cu-mediated indole alkylation tolerated a variety of substituents both on the indole nucleophile, as well as on the cyclic sulfamidate, providing the C^3-alkylated indole products in moderate to good yield and excellent regioselectivity. For instance, indoles with either electron-donating or electron-withdrawing substituents participated in the reaction well (Table 2, **6b**−**6g**), and sterically demanding substrates also worked reasonably well (**6h** and **6i**).

Table 2. Indole Substrate Scope[a]

product			isolated yield (%)	C^3/N^1 ratio[b]
	**6a**		76 (> 99% ee)	97:3
	**6b**	R = Me	73	95:5
	6c	Ph	82	97:3
	6d	Cl	60	96:4
	6e	OMe	92	97:3
	6f	CF_3	47	96:4
	**6g**		68	97:3
	**6h**	R = Me	71	99:1
	6i	Ph	51	98:2
	**6j**		8	98:2

[a]Standard conditions: MeMgCl (130 mol %, 3 M in THF), indole (150 mol %), CuCl (130 mol %) in DCM, 0 °C, followed by **5a** (100 mol %) in DCM (0.2−0.5 mol/L), −20 °C. [b]As determined by HPLC analysis of the crude products.

On the other hand, azaindoles generally are poor substrates. Under standard reaction conditions, 6-azaindole provided only 8% of the alkylation product, albeit with comparable regioselectivity (**6j**). Other azaindoles, such as indazole and 7-azaindole, failed to produce any of the desired alkylated products.

Gratifyingly, a variety of sulfamidates were tested in the reaction successfully. Both aryl- and alkyl-substituted sulfamidates, prepared in a two-step sequence from the corresponding amino alcohols, were converted smoothly to the respective α-substituted chiral tryptamines (**6k**−**6q**).[12] Similarly, six-membered cyclic sulfamidate also participated in the alkylation well, producing a homologated tryptamine in good yield and regioselectivity (**6r**). Note that this alkylation process can be also applied to gain access to β-substituted, and α,β-disubstituted tryptamines (**6s**, **6t**).[13] In these cases, the indole nucleophile added to the corresponding cyclic sulfamidate with the inversion of stereochemistry at the carbon-bearing oxygen with complete stereospecificity.[14] For instance, the reaction with the *cis*-aminoindanol-derived cyclic sulfamidate led to

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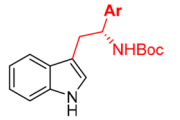
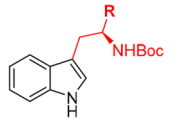
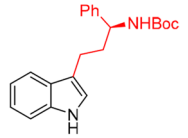
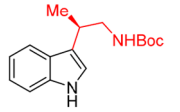
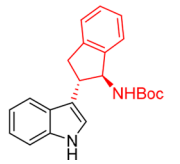
Table 3. Cyclic Sulfamidate Substrate Scope[a]

product		isolated yield (%)	C^3/N^1 ratio[b]
	**6k** Ar = Ph	71	97:3
	6l 4-MeO-Ph	69	98:2
	6m 3-F-Ph	72	99:1
	6n 3-CF_3-Ph	79	98:2
	**6o** R = Me	70	99:1
	6p 2-propyl	59	94:6
	6q c-propyl	65	99:1
	**6r**	73	98:2
	**6s**	78	93:7
	**6t**	54	95:5

[a]Standard conditions: MeMgCl (130 mol %, 3 M in THF), indole (150 mol %), CuCl (130 mol %) in DCM, 0 °C, followed by **5a** (100 mol %) in DCM (0.2−0.5 mol/L), −20 °C. [b]As determined by HPLC analysis of the crude products.

trans-1-amino-2-indolylindane (**6t**), which was confirmed by X-ray crystallographic analysis (see Figure 2).[15]

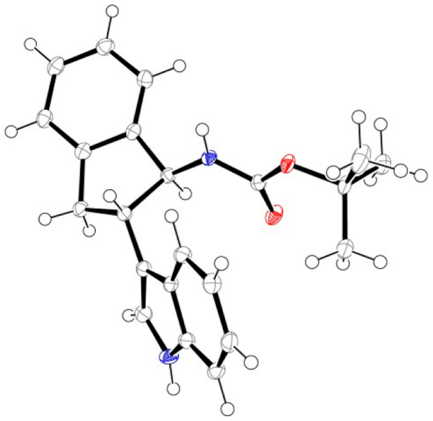
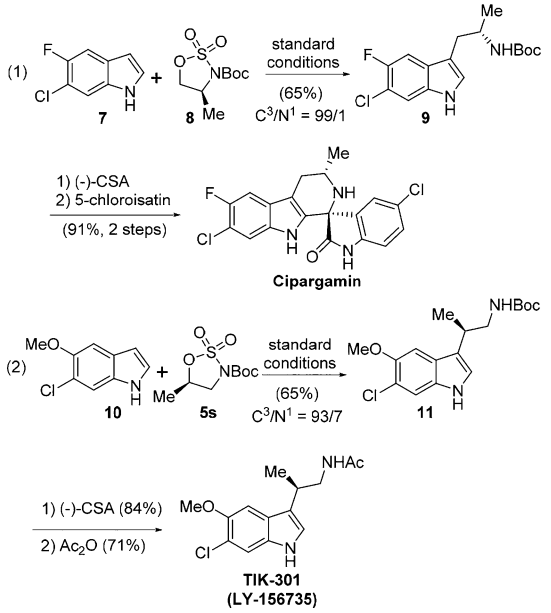


Figure 2. X-ray structure of **6t**.

The utility of this alkylation process was next demonstrated by converting the chiral tryptamine product to tetrahydro-*β*-carbolines by using the Pictet−Spengler reaction.[16] For instance, the chiral tryptamine **9**, derived from 5-fluoro-6-chloroindole, could be readily converted to cipargamin, which is a potent inhibitor of a parasite plasma membrane Na^+-ATPase that regulates sodium and osmotic homeostasis.[17] The alkylation was achieved to provide the intermediate **9** in 65% yield with 99:1 regioselectivity, and Boc removal/Pictet−Spengler reaction completed the synthesis in 91% yield (Scheme 2, eq 1). The versatility of this process was further

Scheme 2. Synthesis of Cipargamin and TIK-301



exemplified in a practical synthesis of a *β*-substituted tryptamine-based investigational melatonin agonist, TIK-301.[18] This time, the alkylation product **11** was smoothly converted to the target product after a simple *N*-acyl group swap. This three-step sequence compares favorably with previous syntheses (see Scheme 2, eq 2).[19]

In summary, we successfully developed a practical synthesis of chiral tryptamines using unprotected indole and chiral cyclic sulfamidates as starting materials. Careful optimization of base and Cu additive led to a simple protocol allowing the desired alkylation at the C^3-position of indole with high regioselectivity and good yield with a range of substrates. Considering the significance of its product structural class, and simplicity of the reaction conditions, we believe this method will find broader application in drug discovery and development.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02335.

Full experimental details and characterization data, including X-ray crystallography data (PDF)

X-ray crystal structure of compound **6t** (Figure S1); crystal data and structure refinement for **6t** (Table S1); atomic coordinates (× 10^4) and equivalent isotropic displacement parameters (× 10^3 Å^2) for **6t** (Table S2); bond lengths (Å) and angles (°) for **6t** (Table S3); anisotropic displacement parameters (× 10^3 Å^2) for **6t** (Table S4); and hydrogen coordinates (× 10^4) and isotropic displacement parameters (× 10^3 Å^2) for **6t** (Table S5) (PDF)

Accession Codes

CCDC 1857975 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge

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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, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(11) We found that chlorinated solvents such as DCM or DCE worked best in the reaction, although many other solvents were also usable including THF, 1,4-dioxane, and DME. In later solvents, however, the reaction mixture tended to form thick slurries, making proper agitation difficult.

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