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KOH-mediated stereoselective alkylation of 3-bromooxindoles for the synthesis of 3,3′-disubstituted oxindoles with two contiguous all carbon quaternary centres†

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The stereoselective synthesis of 3,3′-disubstituted oxindoles having all-carbon quaternary stereocenters has been achieved using KOH as a base with an excellent diastereomeric ratio (98 : 2). The practicability of the present methodology has been validated with the synthesis of a series of substrates in good to excellent yields. The aesthetic simplicity, accessibility, and eco-friendly base (KOH) have prompted the broader application of the present methodology in organic synthesis.

Introduction

Indoline scaffolds with a C3 all-carbon quaternary stereocenter are one of the most commonly observed heterocyclic scaffolds in nature.[1] While the unique C3 stereocenter imparts unmatched bioactivity, it also poses synthetic hardship.[2] The quaternary stereocenter is challenging to recreate due to the substituents on the carbon center that cause high steric repulsions.[2a] Even more challenging is the generation of a vicinal all-carbon quaternary stereocenter.[2b] Despite many efforts, only a limited number of approaches such as alkylation[3] and cycloaddition[4] reactions have been successfully used for the synthesis of such structural motifs to date. One approach that has been recently used is the formation of *o*-azaxylylenes from 3-haloindoles as an intermediate and its exploration in various transformations that can provide direct access to 3-functionalized 2-oxindole derivatives.[5] While the reaction has been developed for the non-stereoselective synthesis of 3-functionalized 2-oxindole, the diastereoselective version is yet to be developed. Recently, several base promoted approaches where carbon nucleophiles and heteroatom-based nucleophiles have been added to the *o*-azaxylylenes have been reported (Fig. 1).[5,6] Interestingly, while it is easier to install single stereocenters on the o-azaxylylenes,[7] installing contiguous stereocenters is quite a herculean task and relatively less explored. In addition, an alternative method to generate the carbon nucleophile can be by simple dearomatization of indoles;[8] however, due to the planar structure of indole, the interaction with the electrophile becomes challenging. The indole dearomatization strategy was first introduced in 1954 by Woodward to synthesize indolenine type scaffolds using Pictet Spengler reaction.[9] Further development in indole dearomatization remained dormant for about three decades till Magnus and Kuehne demonstrated the efficacy of indole dearomatization in the total synthesis of strychnos alkaloids using transannular Mannich reaction.[10] Later on, various synthetic methodologies were developed using indole dearomatization for the total synthesis of natural products and industrially essential molecules.[8e] Among these, alkylative dearomatization of indole has aroused specific interest due to its utility in the synthesis of indole alkaloids containing a C3 all-carbon quaternary center. A thorough literature

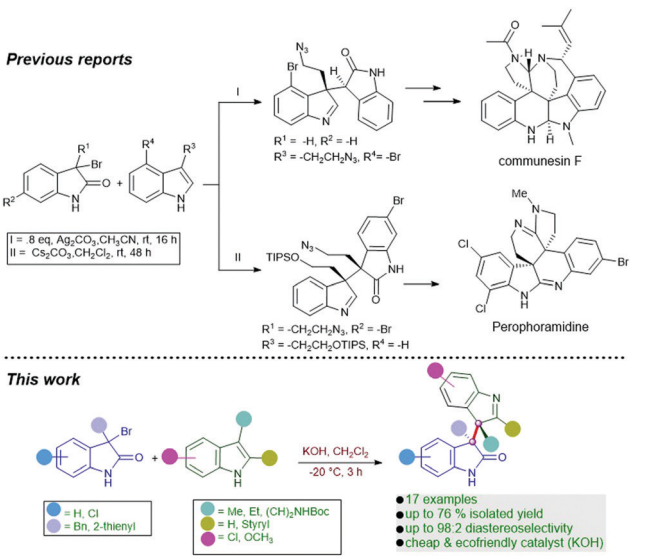

Fig. 1 Methods for the synthesis of 3,3′-dialkyl substituted oxindoles.

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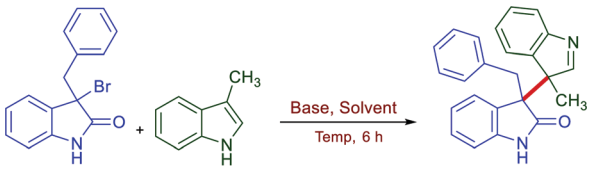
survey suggests that even with a demanding synthetic utility of alkylative dearomatization, only a few reports are witnessed. For instance, in 2004, Funk and co-workers reported the synthesis of perophoramidine using the alkylative dearomatization strategy, and later in 2012, the synthesis of communesin-F was also reported following the same protocol.[6b,g] Later in 2016, Bisai and co-workers reported the synthesis of dimeric 2-oxindoles consisiting of a vicinal all-carbon quaternary stereocenter, which is an active intermediate in the total synthesis of (+)-folicanthine.[6e] Recently, the Feng group have reported the synthesis of β-alkyl nitriles from dearomatization of indol-2-ones having two contiguous stereocentres that provide easy access to the synthesis of pyrroloindolines.[6c] Although the present literature precedences demonstrate that such Michael addition and similar azaxylylene addition reactions are quite extensively used in organic transformation utilizing a metal catalyst, the development of a more economical and environmentally benign approach is still awaited. We believe that a more economical version will have a tremendous impact as commonly used reactions generate more toxic and difficult to dispose off waste in large quantities over scarce reactions that may not generate such waste in any significant quantities. Hence the development of more novel and general synthetic methodologies toward such structural motifs is urgently needed. Herein we report the synthesis of 3, 3′-disubstituted oxindoles having all-carbon quaternary stereocenters using a cheap, readily available, and eco-friendly base KOH.

Table 1 Optimization of the reaction conditions[a]



1a 2a 3a

Entry	Base	Solvent	Temp (°C)	Yield[b] (%)	dr[c] (anti/syn)
1	DIPEA	CPME	r.t.	51	60 : 40
2	DBU	CPME	r.t.	46	60 : 40
3	DABCO	CPME	r.t.	n.d	—
4	K_3PO_4	CPME	r.t.	65	78 : 22
5	$Na_3PO_4{\cdot}12H_2O$	CPME	r.t.	59	65 : 35
6	Cs_2CO_3	CPME	r.t.	62	74 : 26
7	DIPEA	CH_2Cl_2	r.t.	55	60 : 40
8	K_3PO_4	CH_2Cl_2	r.t.	68	77 : 23
9	Cs_2CO_3	CH_2Cl_2	r.t.	78	80 : 20
10[d]	KO*t*Bu	CH_2Cl_2	r.t.	n.d	—
11[d]	KOH	CH_2Cl_2	r.t.	60	85 : 15
12[d]	KOH	CH_2Cl_2	0	70	93 : 7
13[d]	KOH	CH_2Cl_2	−10	70	93 : 7
14[d]	**KOH**	**CH_2Cl_2**	**−20**	**76**	**97 : 3**
15[d]	KOH	CH_2Cl_2	−40	71	95 : 5
16[d]	KOH	C_6H_{14}	−20	n.d.	—
17[d]	KOH	PhMe	−20	45	93 : 7

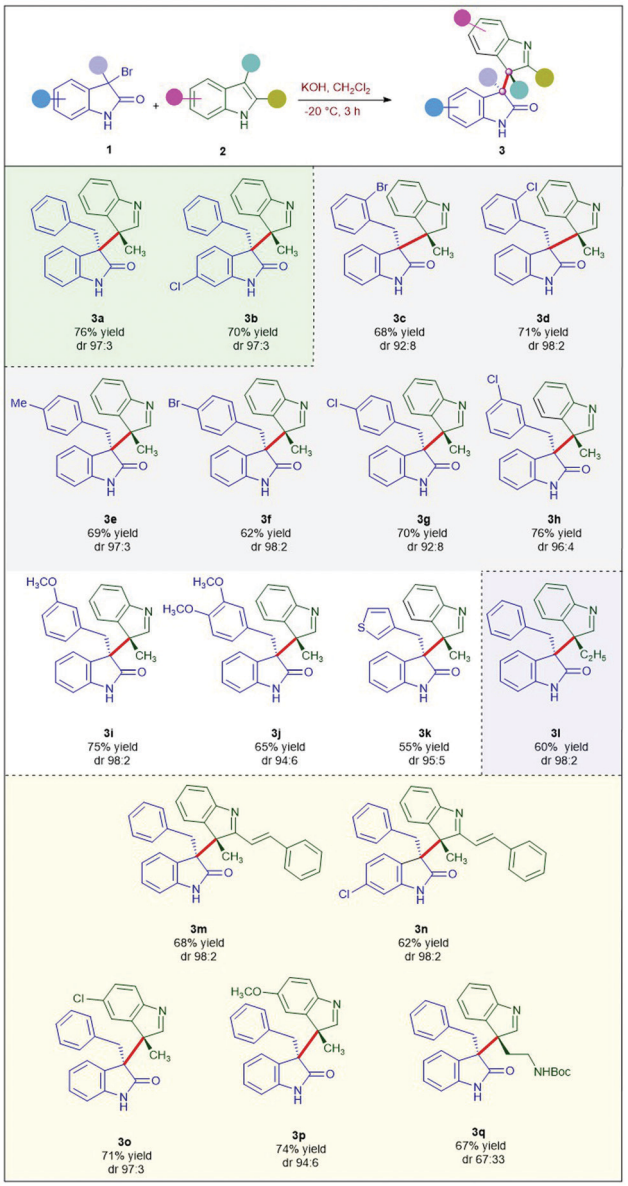
[a] All reactions were performed with **1a** (0.2 mmol), **2a** (0.24 mmol), and base (0.4 mmol) in solvent (2.0 mL) for 6 h. [b] Isolated yield. [c] Diastereomeric ratios were determined by ^{1}H NMR of the crude reaction mixtures. [d] Stirred for 3 h.

Result and discussion

We started our investigation by a model reaction between 3-benzyl-3-bromooxindole **1a** and 3-methylindole **2a** in CPME (cyclopentyl methyl ether) as a solvent and using DIPEA as a base at room temperature. The reaction proceeded smoothly to give the desired product **3a** in 51% yield with a diastereomeric ratio (dr) of 60 : 40 (Table 1, entry 1). Furthermore, the reaction was examined with a hindered base such as DBU; however, a decrease in reactivity was observed (Table 1, entry 2). When the reaction was carried out with DABCO as a base, no product formation was observed. (Table 1, entry 3). In the presence of inorganic bases such as K_3PO_4, $Na_3PO_4{\cdot}12H_2O$, and Cs_2CO_3 only a substantial improvement in the dr of the adduct **3a** with moderate yield was observed (Table 1, entries 4–6). When the solvent was changed from CPME to DCM, no considerable change in the reactivity and selectivity of the reaction was observed (Table 1, entries 7 and 8). On using Cs_2CO_3 as a base in DCM, the reaction yielded the desired product **3a** in 78% yield with 80 : 20 dr (Table 1, entry 9). Interestingly, sterically hindered non-nucleophilic bases like KO^{t}Bu failed to catalyze the reaction, and no product formation was observed (Table 1, entry 10). However, the other strong alkali metal base, KOH, showed better results for the stereoselective alkylation of 3-bromooxindole. By using KOH as a base, a significant reduction in the reaction time and improvement in dr were observed. The reaction was completed in half the reaction time (3 h) to afford **3a** in 60% yield with 85 : 15 dr (Table 1, entry 11). With KOH as an optimal base, the reaction temperature was screened to achieve the best reaction yields. By decreasing the reaction temperature to 0 °C, an increase in reactivity and selectivity of the reaction was observed with 70% yield and 93 : 7 dr (Table 1, entry 12). Decreasing the reaction temperature to −20 °C results in the formation of **3a** in 76% yield with 97 : 3 dr (Table 1, entry 14), and decreasing the reaction temperature to −40 °C affects the reaction yields and dr negatively (Table 1, entry 15). Various solvents were also screened for improvement in yields, and dr. However, a hydrocarbon solvent like hexane did not yield any product formation (Table 1, entry 16), while toluene afforded good diastereoselectivity (93 : 7) with poor reaction yield (Table 1, entry 17). Conclusively, using KOH as a base in DCM solvent at −20 °C affords the best reaction outcome for the stereoablative alkylation of 3-benzyl-3-bromooxindole using 3-methylindole to afford **3a** with 76% yield and 97 : 3 dr. Furthermore, the substrate scope has been examined using the above-mentioned reaction standards unless otherwise noted.

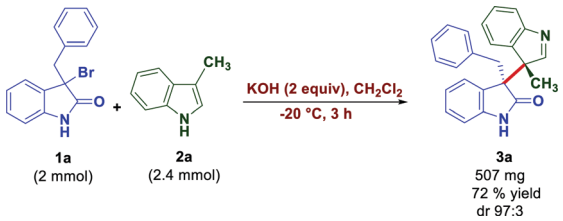
Having the optimized reaction conditions in hand, the substrate scope has been explored using various 3-substituted-3-bromooxindoles. The reaction proceeds smoothly under standard reaction conditions concerning both electron-donating and electron-withdrawing groups (*-ortho*, *-meta* and *-para* position) to afford their corresponding products in good to excellent yields and dr (Table 2, entries **3a**–**3j**). Notably, no dehalogenation has been observed in the case of halogenated oxindoles (**3b**–**d**) that enables the further elaboration of the molecular skeleton using

Table 2 Stereoablative alkylation of various 3-bromooxindoles **1** with various substituted indoles **2**[abc]



[a] All reactions were carried out with **1** (0.2 mmol), **2a** (0.24 mmol), and KOH (0.4 mmol) in CH_2Cl_2 (2.0 mL) at −20 °C for 3 h. [b] Isolated yield. [c] Diastereomeric ratios determined by ^{1}H NMR of crude reaction mixtures.

transition metal-based coupling reactions. The relative stereochemistry of **3c** was assigned to be anti- by single-crystal X-ray analysis (see ESI† for details). Interestingly, the heteroaryl group substituted oxindoles gave a slightly lower yield (55%) with 95 : 5 dr as compared to its other aryl-substituted analogs. Similarly, the C3 substitution on indole also affects the yields of reaction and results in a subsequent decrease in the reaction yield (60%, 98 : 2 dr) on changing the substituent from methyl to ethyl (**3l**). After the successful synthesis of substrates concerning different substitutions on oxindole, the effect of substitution on the C2 position of indoles was further examined on the reaction yields and dr. Delightfully, the C2, C3 disubstituted indoles also react under

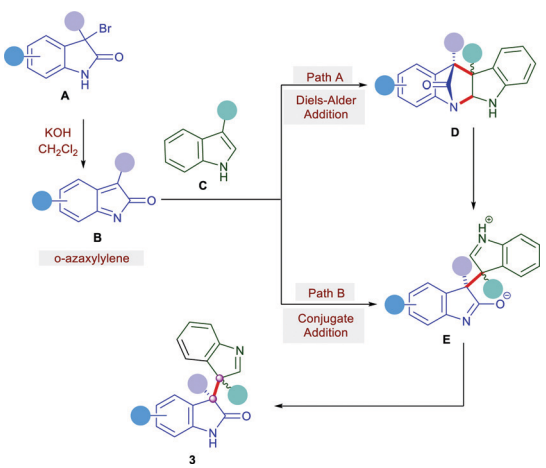


Scheme 1 Gram scale alkylation reaction.

optimized reaction conditions to afford their corresponding products in good yields (62–68%) with 98 : 2 dr (Table 2, entries **3m–3n**). The indoles bearing –Cl or –OMe groups on the phenyl ring of indole also reacted smoothly under the optimised reaction conditions and afforded their corresponding products in acceptable yields and excellent dr (97 : 3). Furthermore, the steric effect of bulky substituents at the C3 position of indole was examined using 3-isopropyl indole as a model substrate. Unfortunately, the reaction did not proceed under the optimized reaction conditions, and starting materials were recovered successfully. However, the *N*-Boc protected 1*H*-indole 3-ethylamine afforded the corresponding product **3q** in 67% yields with lower dr value. The decrease in the reaction yields might be attributed to the steric effect of the –alkylNHBoc group. Conclusively, the steric effect on the C3 position of indole significantly affected its reactivity when a bulkier group than methyl was imposed.

Furthermore, the gram scale alkylation of **1a** was done by treating 2 mmol of **1a** with 2.4 mmol of **2a** yielding the product **3a** in 71% yield and without deterioration in diastereoselectivity (Scheme 1).

Finally, a plausible reaction pathway has been proposed based on literature precedent[6b,g] for the stereoablative alkylation of bromooxindoles with indoles (Scheme 2). The first step involves the formation of an *o*-azaxylylene **B** intermediate from 3-bromooxindole **A** in the presence of a base (KOH). The intermediate **B** undergoes conjugate addition[11] reaction with indole **C** to give the intermediate **E** that undergoes intramolecular proton abstraction to give final product **3**. Notably, the intermediate **B** might undergo Diels–Alders reaction with



Scheme 2 Plausible reaction mechanism.

indole **C** to give the intermediate **D** that undergoes ring opening to give intermediate **E** and finally undergoes intramolecular proton abstraction to give the final product **3**.

Conclusions

In conclusion, we have developed a KOH mediated strategy for the stereoselective synthesis of 3,3′-disubstituted oxindoles having all-carbon quaternary stereocenters from 3-bromooxindoles and 3-substituted indoles in good to excellent yields and diastereoselectivity up to 98 : 2. The substrate scope has been examined concerning different substitutions on 3-bromooxindoles, and 3-methyl indole, which resulted in their corresponding products in good yields and diastereotopic ratio that indeed enables the synthesis of a library of heteroaromatics.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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