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# Silver-Mediated Intramolecular Friedel–Crafts-Type Cyclizations of 2-Benzyloxy-3-bromoindolines: Synthesis of Isochromeno[3,4-*b*]indolines and 3-Arylindoles

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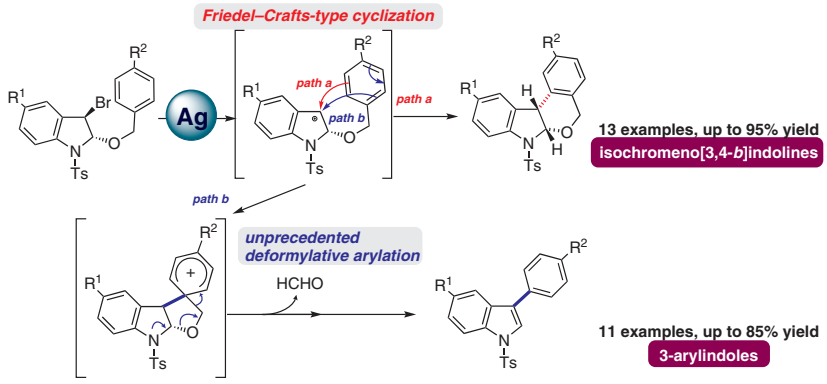


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**Abstract** We disclose a silver-mediated intramolecular Friedel–Crafts-type cyclization of 2-benzyloxy-3-bromoindolines to afford an untapped family of isochromeno[3,4-*b*]indolines and 3-arylindoles, in which deformylative arylation of 2-(4-methoxybenzyloxy)-3-bromoindolines is reported for the first time. The isochromeno[3,4-*b*]indolines can be readily transformed into other heterocyclic moieties.

**Key words** Friedel–Crafts, cyclization, isochromeno[3,4-*b*]indolines, deformylative arylation, 3-arylindoles, silver

Chromenoindolines and isochromenoindolines form an important group of pharmacologically active compounds displaying, for example, antimalarial activity,[1] anticancer activity,[2] antiplasmodial activity toward the chloroquine-resistant strain FcB1 of *Plasmodium falciparum*,[3] cytotoxicity against KB, L1210 cells,[4] and vincristine resistant human KB (Figure 1).[5] Recently, many useful approaches to chromeno[2,3-*b*]indolines have been explored to develop more potent biologically active compounds.[6] On the other hand, the synthesis of isochromeno[3,4-*b*]indolines has scarcely developed until recently because of their complex structures including 3-arylindolines.[7]

In 2017, Vincent and co-workers reported a silver-mediated oxidative coupling of indoles and tetrahydro-β-carbolines with 2,3-dihydroxybenzoic acids for the construction of isochromeno[3,4-*b*]indolines, affording the total synthesis of voacalgine A and bipleiophylline (Scheme 1A).[8]

As a catalytic version of the oxidative coupling, Chen and co-workers developed the Fe-mediated oxidative coupling of indoles with 2,3-dihydroxybenzoic acids (Scheme 1B).[9] These reactions require 2,3-disubstituted or 3-substituted indoles and 2,3-dihydroxybenzoic acids due to the formation of an orthoquinone intermediate.

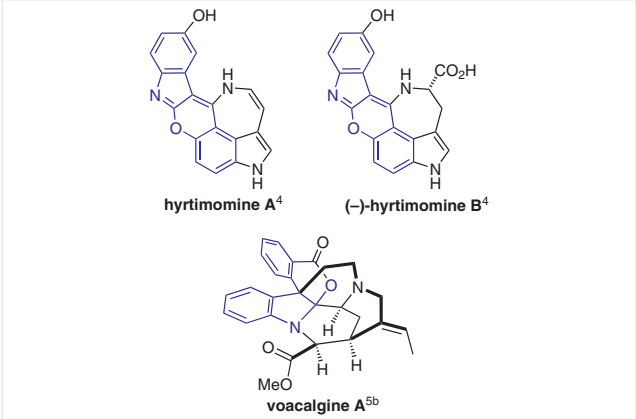


**Figure 1** Selected chromenoindolines and isochromenoindolines alkaloids

Apparently, these features restricted the access to various substituted isochromeno[3,4-*b*]indolines. Accordingly, the synthesis of isochromeno[3,4-*b*]indolines remains unexploited using these reactions and simple starting materials.

As part of our ongoing investigations focused on the indole chemistry,[10] we were eager to tackle the challenges of exploring a concise construction of isochromeno[3,4-*b*]indolines bearing a variety of substituents because it could lead to pharmacologically active compounds. Recently, we

 
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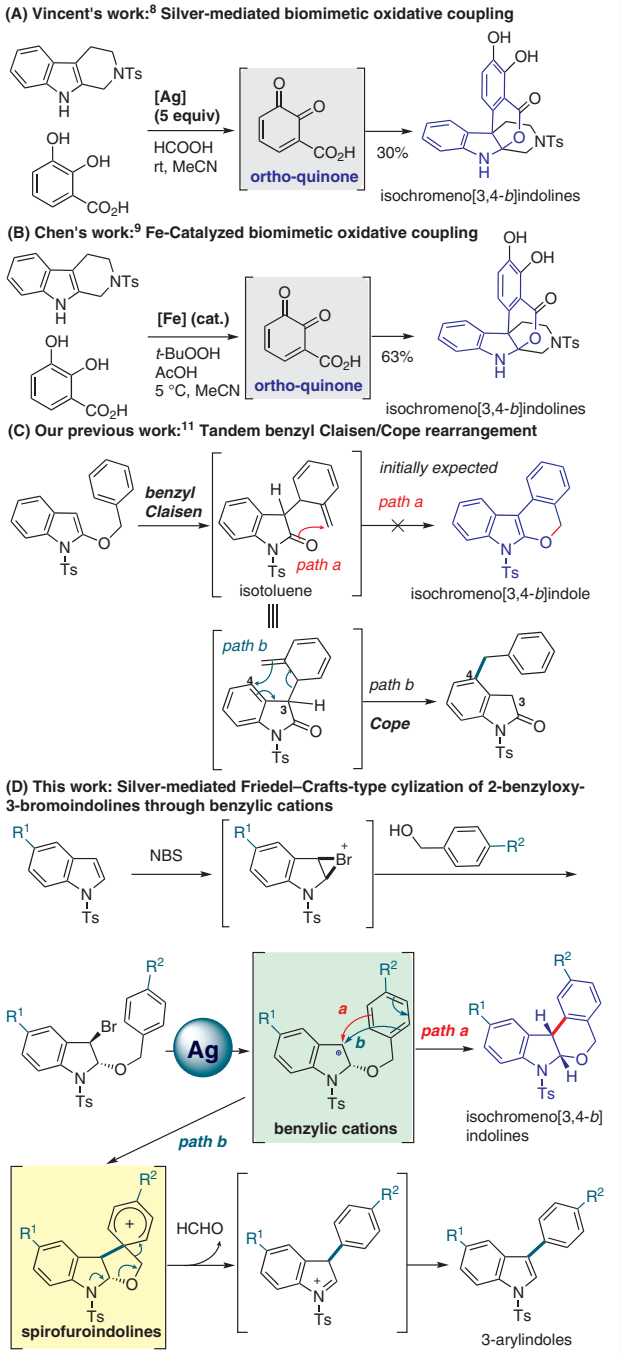
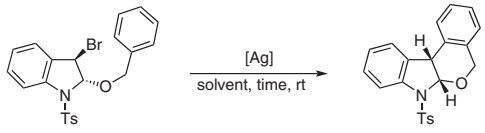



**Scheme 1** Previous work on the synthesis of isochromeno[3,4-*b*]indolines

have developed a direct C4 benzylation of indoles utilizing 2-benzyloxyindoles, affording 4-benzyl-2-oxindoles (Scheme 1C).[11] This reaction involves the formation of isotoluene intermediates in situ via a benzyl Claisen rearrangement, which undergo Cope rearrangement and aromatization (Scheme 1C, path b). In these investigations, we concluded that the initially expected isochromeno[3,4-*b*]indoles could not be obtained through the isotoluene intermediate followed by cyclization (Scheme 1C, path a). The failure of the benzyl Claisen rearrangement/cyclization protocol to construct chromeno[3,4-*b*]indole structures led us to study a silver-mediated Friedel–Crafts-type cyclization of 3-bromoindolines.

It is well known that the halogenophilicity of the silver salts toward $Csp^3$–halogen bonds can enable mild activation and high functional group compatibility in the intermolecular Friedel–Crafts reaction of 3-haloindolines with nucleophiles, as reported by Movassaghi,[12] Qin,[13] Ye,[14] Vincent,[15] and Tokuyama.[16] We envisioned that a silver-mediated intramolecular Friedel–Crafts-type cyclization of 2-benzyloxy-3-bromoindolines would allow access to isochromeno[3,4-*b*]indolines. Herein, we describe a novel construction of isochromeno[3,4-*b*]indolines by a silver-mediated Friedel–Crafts-type cyclization of easily available starting materials (Scheme 1D, path a). An electron-donating group on the benzyl moiety was shown to alter the normal reactivity of the Friedel–Crafts-type cyclization, affording 3-

**Table 1** Reaction Condition Optimization[a]




**1aa** **2aa**

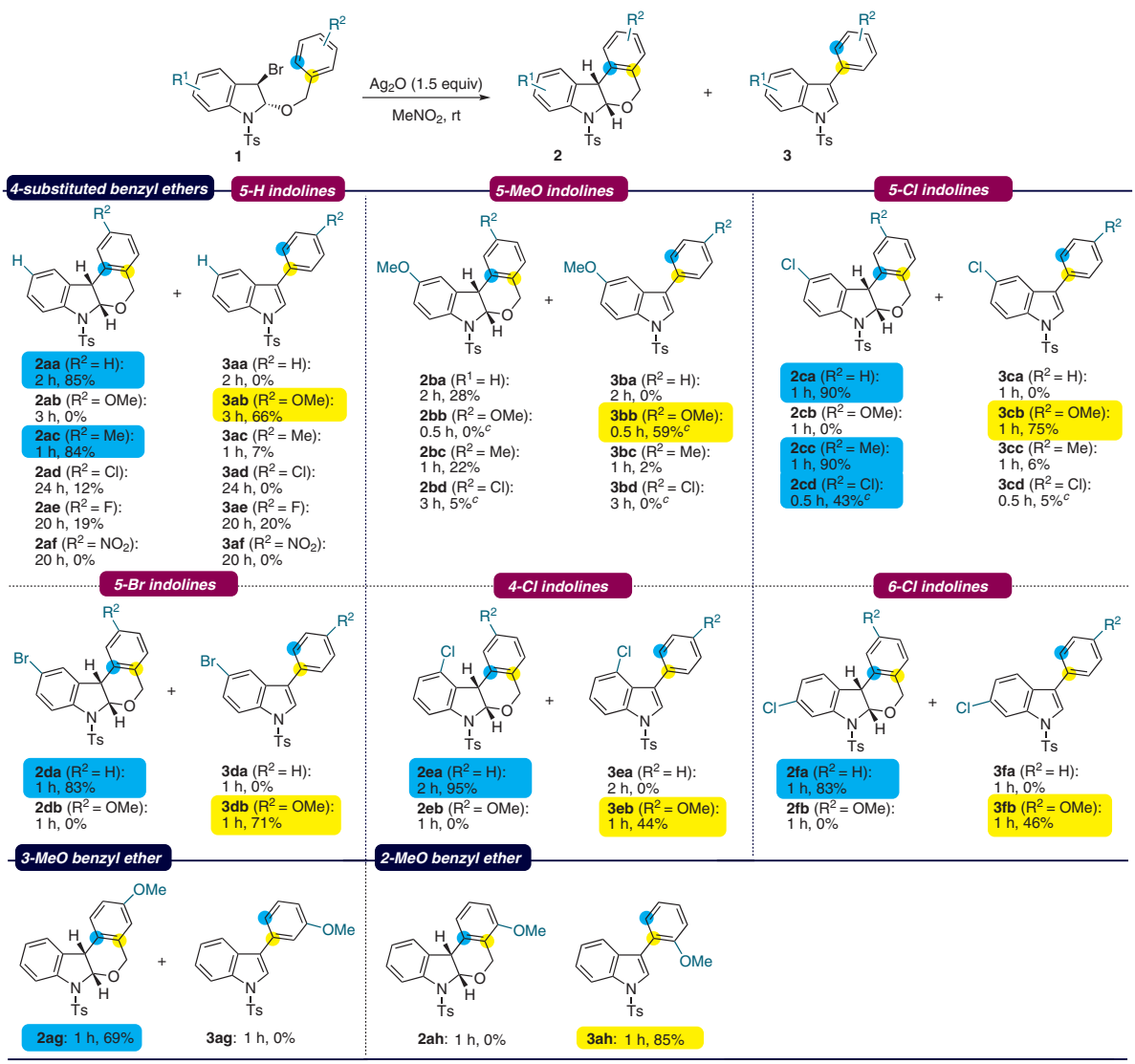
| Entry | Ag (equiv) | Solvent (mL) | Time (h) | Yield (%)[b] |
|---|---|---|---|---|
| 1 | $Ag_2O$ (5) | EtOAc (5) | 0.5 | 62 |
| 2 | $Ag_2O$ (5) | $CF_3C_6H_5$ (5) | 3 | 60 |
| 3 | $Ag_2O$ (5) | toluene (5) | 48 | 62 |
| 4 | $Ag_2O$ (5) | MeCN (5) | 48 | 21 |
| 5 | $Ag_2O$ (5) | $CHCl_3$ (5) | 0.5 | 42 |
| 6 | $Ag_2O$ (5) | TFE (5) | 1 | 66 |
| **7** | **$Ag_2O$ (5)** | **$MeNO_2$ (5)** | **0.5** | **85** |
| 8 | $Ag_2CO_3$ (5) | $MeNO_2$ (5) | 1 | 77 |
| 9 | $AgNTf_2$ (5) | $MeNO_2$ (5) | 2 | 0 |
| 10 | AgCN (5) | $MeNO_2$ (5) | 24 | 29 |
| 11 | AgOTf (5) | $MeNO_2$ (5) | 1 | 0 |
| 12 | $AgPF_6$ (5) | $MeNO_2$ (5) | 0.5 | 36 |
| 13 | $Ag_2O$ (5) | $MeNO_2$ (2) | 0.5 | 86 |
| 14 | $Ag_2O$ (3) | $MeNO_2$ (2) | 2 | 85 |
| **15** | **$Ag_2O$ (1.5)** | **$MeNO_2$ (2)** | **2** | **85** |
| 16 | $Ag_2O$ (0.5) | $MeNO_2$ (2) | 24 | 45 |
| 17 | – | $MeNO_2$ (2) | 24 | 0 |

[a] Reaction conditions: **1aa** (0.2 mmol), Ag salt, solvent, r.t.
[b] Isolated yields.
[c] Complex mixtures.

arylindoles via an unprecedented *ipso*-attack on the benzene ring/deformylative arylation sequences (Scheme 1D, path b).

Initially, the reaction was carried out using *N*-Ts 2-benzyloxy-3-bromoindoline (**1aa**)[11] and 5 equiv of $Ag_2O$ in EtOAc at room temperature. As expected, the reaction proceeded smoothly to afford isochromeno[3,4-*b*]indoline **2aa** in 62% yield (Table 1, entry 1). To improve the yield of **2aa**, optimization of the protocol by replacing $Ag_2O$ with other silver salts, replacing EtOAc with other solvents, and modulating the equivalent of silver salts and the solvent concentration was conducted. The most efficient solvent was $MeNO_2$ (entries 1–7). $Ag_2O$ was the best silver salt for the transformation (entry 7), while all other silver salts studied, such as $Ag_2CO_3$, $AgNTf_2$, $AgNO_3$, AgOTf, and $AgPF_6$, gave lower yields (entries 8–12). Finally, when 1.5 equivalent of $Ag_2O$ was used in $MeNO_2$ (0.1 M), good conversion into **2aa** was observed (entries 13–16). A control experiment without the silver salt did not give product **2aa** (entry 17).

With the optimized conditions identified, the scope of the reaction was investigated by using a variety of 2-benzyloxy-3-bromoindolines **1** (Scheme 2). In general, a diverse range of substrates **1** were successfully used to afford isochromeno[3,4-*b*]indolines **2** up to 95% yield, although the electronic nature of the substituents on the benzene-ring at **1** had an influence on the reaction efficiency. An electron-donating group on the indole ring was not fully tolerated in the Friedel–Crafts-type process (**2ba**, **2bc** and **2bd**), while electron-withdrawing groups were compatible (**2ca**, **2cc**, **2cd**, **2da**, **2ea**, and **2fa**). Specifically, substrates with chloro



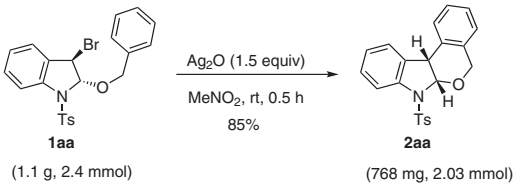

**Scheme 2** Substrate scope of silver-mediated Friedel–Crafts-type cyclization of 2-benzyloxy-3-bromoindolines. *Reagents and conditions*: **1** (0.2 mmol) and $Ag_2O$ (0.3 mmol, 1.5 equiv) in $MeNO_2$ (2 mL) at r.t. (isolated yields given). [a] $Ag_2O$ (1.0 mmol, 5 equiv) was used.

or bromo substituents were tolerated in the silver-mediated transformation. The halogen functional group allowed further synthetic manipulations of the products through transition-metal-catalyzed cross-couplings. A 4-methoxy group on the benzyl moiety has been shown to alter the normal reactivity of the Friedel–Crafts-type cyclization, affording 3-arylindoles **3** with release of HCHO (**3ab**, **3bb**, **3cb**, **3db**, **3eb**, **3fb**, and **3ah**).

Notably, a reverse regioselectivity was observed (**2ag**, *ortho*-attack) when a 3-methoxy substrate **1ag** was used. These results suggest that the *para*- or *ortho*-position to the $CH_2O$-group reacted to afford the arylated products **3** in this transformation. The deformylative arylation has been scarcely reported to date[17] in contrast to the decarboxylative arylation.[18,19] To our knowledge, this is the first example of an arylation using benzyl ethers as the arylating reagent. Such 3-arylindoles are of great interest because of their intriguing biological activities.[20]

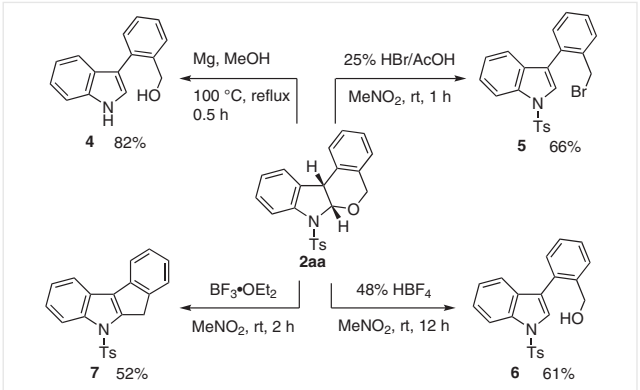
To further show the synthetic use of this transformation, we conducted a 2.4 mmol (**1aa**, 1.1 g) scale reaction (Scheme 3). The gram-scale reaction afforded the desired product **2aa** in 85% yield and the cyclization was as efficient as the 0.2 mmol scale reaction (**2aa**: 85% yield, Scheme 2).




**Scheme 3** Scale-up reaction

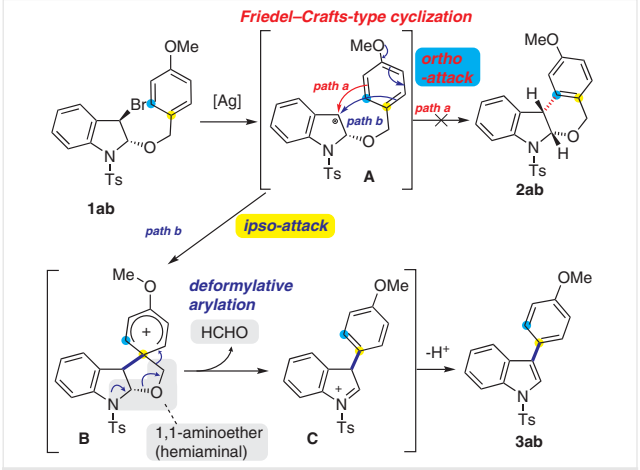
Encouraged by the applicability for the gram-scale reaction, we further explored the synthetic utility of **2aa** in organic synthesis (Scheme 4). The tosyl group of **2aa** could be readily removed upon treatment with Mg powder in methanol under reflux conditions, to give 3-aryllindole **4** in 82% yield. 2-Indolyl benzyl alcohols are utilized as intermediates for electroluminescent hosts.[21] Treatment of **2aa** with HBr or $HBF_4$ led to the formation of **5** or **6** via a ring-opening reaction. Among the acids investigated, $BF_3{\cdot}OEt_2$ afforded dihydroindeno[2,1-*b*]indole **7** in 52% yield through a ring-opening reaction and dehydrative cyclization.

Based on the results presented in Scheme 2 and on previous reports,[22,23] we propose a plausible reaction pathway and deformylation mode to explain the chemistry of the deformylative arylation of **1ab** (Scheme 5). Initially, **1ab** should give carbocation intermediate **A** upon reaction with the silver complex. In pathway (a), *ortho*-attack by the 4-MeO-benzyl moiety to the carbocation may occur to afford **2ab**. In pathway (b), *ipso*-attack by the 4-MeO-benzyl moiety to the carbocation may afford arenium intermediate **B**.[22] Then, to restore the original aromatic structure, this 1,1-




**Scheme 4** Synthetic elaborations of compound **2aa**

aminoether (hemiaminal) **B** undergoes deformylation with the aid of the indole nitrogen to give the 3-arylated product **3ab** through aromatization of indolenium intermediate **C**.[23] Given that the yield of **2ab** is 0%, the substrate **1ab** preferentially favors intermediate **B** due to the stabilization of the arenium intermediate **B** by the methoxy group. Thus, the *ipso*-attack of the intermediate **A** occurs regiospecifically, which generates the intermediate **B** and produces product **3ab**.




**Scheme 5** Plausible mechanism

In summary, we achieved a silver-mediated intramolecular Friedel–Crafts-type cyclization of 2-benzyloxy-3-bromoindolines via the generation of benzyl cation intermediates. This is the first example of a construction of isochromeno[3,4-*b*]indolines without using 2-hydroxybenzoic acids as a substrate. This protocol exhibits a wide substrate scope and proceeds under mild conditions. Furthermore, as a demonstration of the synthetic potential of this protocol, the derivatization of isochromeno[3,4-*b*]indolines was carried out. On the other hand, a methoxy group on the benzyl moiety has been shown to alter the normal reactivity of the

Friedel–Crafts-type cyclization, affording 3-arylindoles via an unprecedented *ipso*-attack on the benzene ring/deformylative arylation sequences. Future efforts will focus on the intermolecular Friedel–Crafts-type cyclization and on the development of an enantioselective variant of the reaction.

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## Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690734.

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