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$Ga(OTf)_3$-Catalyzed Temperature-Controlled Regioselective Friedel−Crafts Alkylation of Trifluoromethylated 3-Indolylmethanols with 2-Substituted Indoles: Divergent Synthesis of Trifluoromethylated Unsymmetrical 3,3′-and 3,6′-Bis(indolyl)methanes

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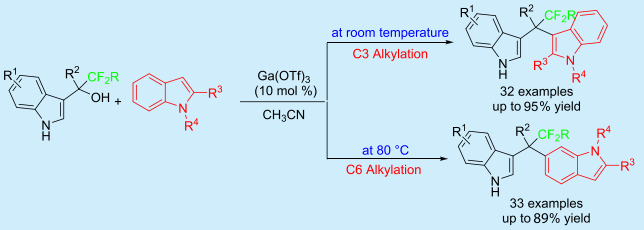
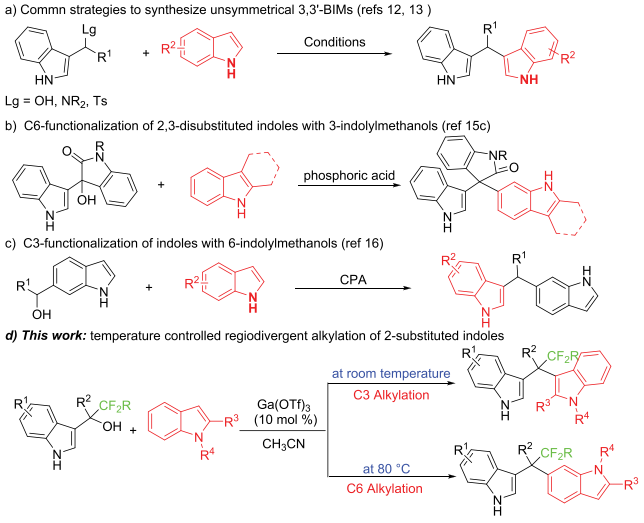
Supporting Information

ABSTRACT: An unprecedented $Ga(OTf)_3$-catalyzed, temperature-controlled regiodivergent alkylation of 2-substituted indoles with trifluoromethylated 3-indolylmethanols is described that provides structurally diverse unsymmetrical 3,3′- and 3,6′-bis(indolyl)methanes with a CF_3-containing quaternary carbon center in good to excellent yields under mild conditions. In addition, this present protocol could be successfully extended to the synthesis of difluoromethylated 3,3′- and 3,6′-bis(indolyl)methanes with excellent efficiency.



Bis(indolyl)methanes (BIMs) represent one of the privileged structural motifs and are ubiquitously present in a myriad of bioactive natural products, pharmaceuticals, and agrochemicals as well as functional materials.[1−8] BIM derivatives have been found to exhibit a broad range of bioactivities,[4] such as antibacterial,[2d,5] antifungal,[6] anti-inflammatory,[7] and anticancer activity.[8] Owing to their versatile biological activities and applications, the synthesis of BIMs has attracted tremendous attention, and numerous efficient methods have been developed. In general, symmetrical 3,3′-BIMs can be readily synthesized from indoles and carbonyl compounds by Lewis or Brønsted acid catalyzed condensation reactions[1b,9] or other processes.[10] However, the synthesis of unsymmetrical BIMs, such as unsymmetrical 3,3′- and 3,6′-BIMs, remains challenging and less explored, especially for the latter. Recently, 3-indolylmethanols have emerged as one of the most versatile pro-electrophiles for constructing 3-indolyl-containing frameworks.[11] Among them, Friedel−Crafts alkylation of easily accessible 3-indolylmethanols or its analogous with indoles has proven to be a powerful and prevailing strategy for the preparation of the 3,3′-BIMs (Scheme 1a).[12,13] However, the majority of these processes are restricted to the tertiary unsymmetrical 3,3′-BIMs, as synthetic methods to efficiently access unsymmetrical 3,3′-BIM scaffolds with a quaternary center are exceedingly rare.[14] Moreover, achieving no C3-selectivity in indole alkylation reactions is also a significant challenge because the C3-position is the most electron-rich carbon center in the indole ring.[15] To overcome the direct C3-selective functionalization of indoles, Shi and coworkers have demonstrated that unsymmetrical 3,6′-BIMs could be accessed from 2,3-disubstituted indoles and 3-indolylmethanols, which provides the first example for

Scheme 1. Strategies to access unsymmetrical 3,3′-and 3,6′-bis(indolyl)methanes



producing 3,6′-BIMs on the basis of C6-selective functionalization of indoles (Scheme 1b).[15c] Very recently, an alternative protocol to 3,6′-BIMs has been realized by utilizing 6-indolylmethanols and indoles in the presence of CPA (Scheme 1c).[16]

On the other hand, the introduction of trifluoromethyl groups (CF_3) into organic frameworks can dramatically

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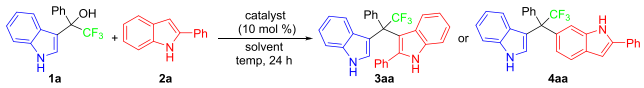
influence their physicochemical and biological properties in comparison with their nonfluorinated analogues.[17] Given this perspective, the development of a new strategy for the efficient construction of trifluoromethylated unsymmetrical 3,3′- and 3,6′-BIMs would be highly valuable, as these pharmacophores may possess novel and interesting bioactivity.

As a part of our continuous efforts in the chemistry of BIMs,[18] we herein present a new and robust protocol to access unsymmetrical 3,3′- and 3,6′-BIMs with a CF_3-containing all-carbon quaternary center through $Ga(OTf)_3$-catalyzed, temperature-controlled regioselective Friedel–Crafts alkylation of trifluoromethylated 3-indolylmethanols with 2-substituted indoles. Furthermore, this method could be successfully extended to the synthesis of difluoromethylated 3,3′- and 3,6′-BIMs with excellent efficiency.

We commenced our studies by employing 2,2,2-trifluoro-1-(1*H*-indol-3-yl)-1-phenylethanol (**1a**) and 2-phenylindole (**2a**) as the model substrates. This study initially revealed that treatment of **1a** and **2a** (1.5 equiv) with 10 mol % of $FeCl_3$ in acetonitrile at room temperature for 24 h led to the formation of **3aa** in 12% yield and the recovery of starting material **1a** in 81% yield (Table 1, entry 1). To increase the product yield of

Table 1. Optimization of Reaction Conditions[a]



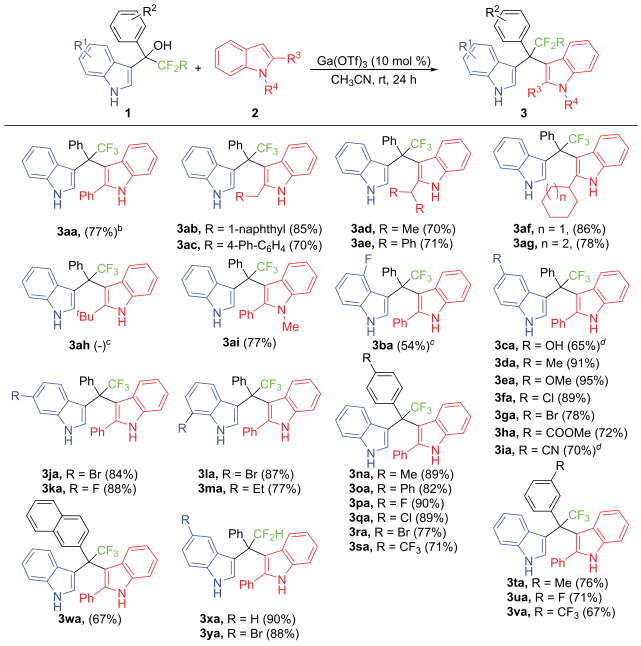
				yield[b] (%)	
entry	catalyst	solvent	temp (°C)	**3aa**	**4aa**
1	$FeCl_3$	CH_3CN	25	12	*c*
2	$FeCl_3$	CH_3CN	80		56
3	$Yb(OTf)_3$	CH_3CN	80		58
4	$In(OTf)_3$	CH_3CN	80		61
5	$Y(OTf)_3$	CH_3CN	80		71
6	$Sc(OTf)_3$	CH_3CN	80		76
7	AgOTf	CH_3CN	80		*d*
8	$Ni(ClO_4)_2$	CH_3CN	80		*d*
9	**$Ga(OTf)_3$**	**CH_3CN**	**80**		**86**
10	$Ga(OTf)_3$	CH_3CN	80		72[e]
11	TfOH	CH_3CN	80		68
12	$Ga(OTf)_3$	toluene	80		56
13	$Ga(OTf)_3$	DCE	80		65
14	$Ga(OTf)_3$	dioxane	80		*d*
15	**$Ga(OTf)_3$**	**CH_3CN**	**25**	**81**	

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.45 mmol), catalyst (10 mol %), solvent (3 mL), 24 h. [b]Isolated yield. [c]**1a** was recovered in 81% yield. [d]No reaction based on TLC analysis and ^1H NMR measurements of the crude reaction mixture. [e]Reaction carried out with **1a** (0.45 mmol) and **2a** (0.3 mmol).

3aa, the reaction was performed at 80 °C for 24 h. Interestingly, the chemoselectivity was completely switched to the formation of C6-functionalization product **4aa** in 56% yield (entry 2). The structure of **3aa** and **4aa** was unambiguously ascertained by NMR measurements and X-ray crystallographic analysis. Encouraged by these promising results, we next examined a variety of other Lewis acid catalysts in an attempt to further improve the yield. Slightly higher yields of **4aa** were observed when $FeCl_3$ was replaced by $Yb(OTf)_3$, $In(OTf)_3$, $Y(OTf)_3$, or $Sc(OTf)_3$ (entries 3–6). However, performing the reaction in the presence of AgOTf or $Ni(ClO_4)_2$ gave no conversion (entries 7 and 8). Gratifyingly, **4aa** could be obtained in 86% yield when the reaction was carried out by using $Ga(OTf)_3$ as the catalyst (entry 9). Varying the ratio of **1a** and **2a** (entry 10) or with TfOH as the catalyst (entry 11) was found to be less effective. Further screening of solvents showed that CH_3CN was the optimal choice (entries 9 and 12–14). Surprisingly, decreasing the reaction temperature from 80 °C to room temperature provided **3aa** as the only product in 81% yield (entry 15). Therefore, reactions of **1a** with **2a** (1.5 equiv) in the presence of 10 mol % of $Ga(OTf)_3$ in CH_3CN at room temperature or 80 °C for 24 h provided the optimum conditions to selectively prepare either 3,3′-BIMs or 3,6′-BIMs, respectively.

With the two optimized reaction conditions to access the 3,3′-BIMs and 3,6′-BIMs in hand, we first sought to evaluate the generality of the former, and the results are summarized in Scheme 2. Overall, the C3-selective FC alkylation conditions

Scheme 2. Regioselective C3-Alkylation of Diverse 2-Substituted Indoles[a]



[a]Reaction conditions: **1** (0.3 mmol), **2** (0.45 mmol), $Ga(OTf)_3$ (10 mol %), CH_3CN (3 mL), room temperature, 24 h. Values within parentheses denote isolated product yields. [b]4 mmol scale. [c]No reaction based on TLC analysis and ^1H NMR measurements of the crude reaction mixture. [d]Reaction time of 48 h.

proved to be broad, producing a diverse array of 3,3′-BIM derivatives bearing a CF_3-containing quaternary center with a variety of substitution patterns in 54–95% yields from the corresponding trifluoromethylated 3-indolylmethanols and 2-substituted indoles. To demonstrate the scalability of the present C3-selective alkylation reaction, a gram-scale reaction of **1a** (4 mmol, 1.165 g) and **2a** (6 mmol) was carried out, affording the desired product **3aa** in 77% yield. Notably, C2-substituted indoles bearing diverse acyclic alkyl (**2b–e**) and cyclic alkyl groups (**2f–g**) and *N*-methyl-2-phenylindole (**2i**) all reacted smoothly with **1a** to produce the corresponding products **3ab–ai** in 70–86% yields. Unfortunately, no reaction was observed when 2-*tert*-butylindole (**2h**) was employed, presumably due to the steric hindrance of the bulky ^{t}Bu group. Subsequently, reactions of 2-phenylindole (**2a**) with 3-

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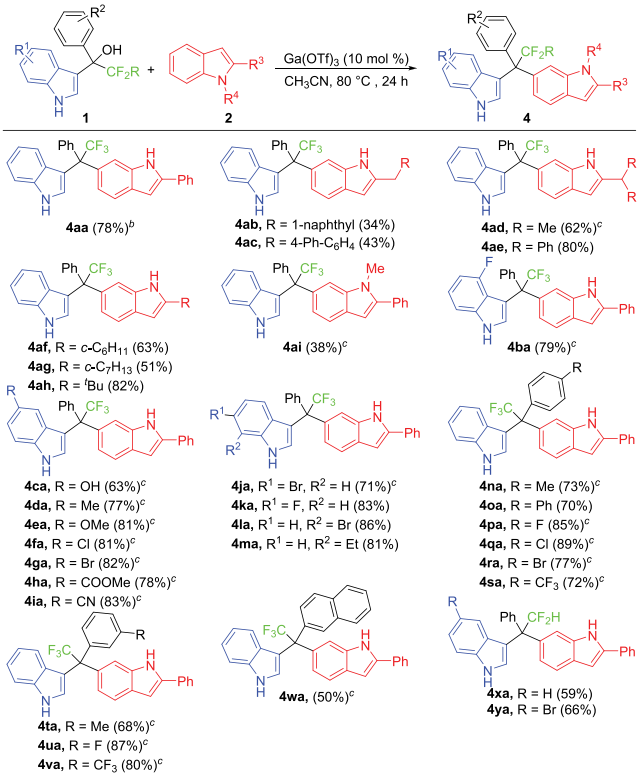
indolylmethanols containing various functional groups, such as halides, Me, Et, OH, OMe, COOMe, and CN at different positions (C4−C7) on the indole moiety, were investigated. The corresponding products **3ba**−**ma** could be furnished in moderate to excellent yields (54−95%), albeit requiring longer reaction times (48 h) for substrates **1b**, **1c**, and **1i**. Meanwhile, 3-indolylmethanols **1** carrying various electron-donating and electron-withdrawing substitutions at the *para*- or *meta*-position of the benzene ring were found to be compatible in the reaction, although the former provided the corresponding products **3na**−**sa** in higher yields than the latter. Moreover, the presence of the 2-naphthyl motif in **1w** was proven to be suitable, with **3wa** being furnished in 67% yield. Remarkably, difluoromethylated 3-indolylmethanols (**1x**, **1y**) were also successfully employed to provide the corresponding products **3xa** and **3ya** in respective yields of 90% and 88%.

Encouraged by the above success, we next examined the scope of the C6-selective Friedel−Crafts alkylation using the same substrates under the optimized conditions (Scheme 3).

Scheme 3. Regioselective C6-Alkylation of Diverse 2-Substituted Indoles[a]

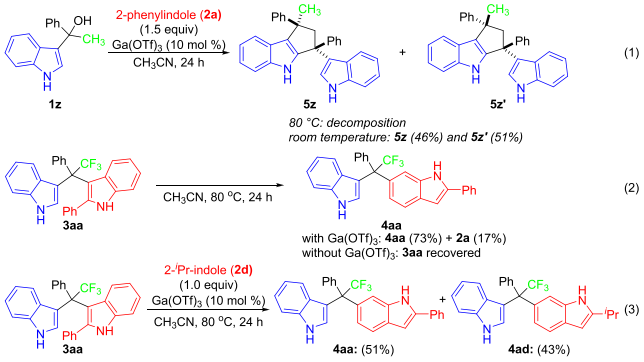


[a]Reaction conditions: **1** (0.3 mmol), **2** (0.45 mmol), $Ga(OTf)_3$ (10 mol %), CH_3CN (3 mL), 80 °C, 24 h. Values within parentheses denote isolated product yields. [b]4 mmol scale. [c]Reaction time of 48 h.

First, we found that the C6-selective alkylation reaction of **1a** (4 mmol scale) with **2a** could be successfully scaled up, affording the desired product **4aa** in a slightly diminished yield of 78% (1.455 g), demonstrating the scalability of the present protocol. The reactions of **1a** with C2-substituted indoles bearing acyclic alkyl groups such as 1-naphthalenylmethyl (**2b**), 4-phenylbenzyl (**2c**), or *N*-methyl-2-phenylindole (**2i**) proceeded less efficiently to give the corresponding products (**4ab**, **4ac**, **4ai**) in lower yields. Intriguingly, C2-substituted indoles possessing various sterically hindered substituents such as isopropyl (**2d**), diphenylmethyl (**2e**), cyclohexyl (**2f**), cycloheptyl (**2g**), and *tert*-butyl (**2h**) all reacted smoothly with **1a** to deliver the corresponding products **4ad**−**ah** in good to excellent yields. Reactions of 3-indolylmethanols containing an electron-withdrawing (F, Cl, Br, COOMe, CN) or electron-donating (OH, Me, Et, OMe) substituent at the C4−C7 positions on the indole moiety were found to proceed well with **2a** to give the corresponding 3,6′-BIMs **4ba**−**ma** in 63−86% yields. Similarly, 3-indolylmethanols possessing either electron-donating (**1n**,**o**,**t**) or electron-withdrawing (**1p**−**s**,**u**−**v**) substituents at the *para*- or *meta*-position of the phenyl ring were found to have a minimal effect on the outcome of the reaction, affording the corresponding 3,6′-BIMs **4na**−**ua** in yields of 68−89%. However, substrates with a pendant hindered 2-naphthyl group, as in **1w**, provided **4wa** in low yield. In addition, difluoromethylated 3-indolylmethanols (**1x**, **1y**) could also react with **2a** smoothly to give the desired products **4xa**−**ya** in moderate to good yields (59−66%).

To gain further insight into the reaction mechanism, several control experiments were performed (Scheme 4). When the

Scheme 4. Control Experiments



nonfluorinated 3-indolylmethanol **1z** and **2a** was subjected to the optimal conditions at 80 °C or room temperature, no desired 3,3′- or 3,6′-BIM products could be obtained; instead, the former gave only decomposition products, and the latter delivered the cyclopentano[*b*]indole **5z** and **5z′** in 46% and 51% yields, respectively (Scheme 4, eq 1).[19] These results indicated that the presence of a CF_3 or CF_2H substituent is crucial for the regioselective alkylation process. Next, exposure of **3aa** to $Ga(OTf)_3$ under the optimal conditions at 80 °C provided **4aa** in 73% yield along with 17% yield of 2-phenylindole (**2a**).

However, the analogous reaction of **3aa** in the absence of $Ga(OTf)_3$ led to its recovery in 95% yield (Scheme 4, eq 2). These results corroborated that **3aa** was most likely involved as the intermediate and ruled out the possibility of a thermally driven rearrangement process. Finally, we investigated the crossover reaction of **3aa** with equimolar 2-^{i}Pr-indole **2d** under the conditions shown in Scheme 4, eq 3. This revealed that the corresponding 3,6′-BIMs **4aa** and **4ad** could be isolated in respective yields of 51 and 43%, suggesting that the conversion of 3,3′-BIMs to 3,6′-BIMs might proceed in an intermolecular manner.

On the basis of the above observations and previous reports,[11−15] a tentative mechanism is proposed as depicted in Scheme 5. With **1a** and **2a** as representative examples, this might involve initial activation of the alcohol substrate by

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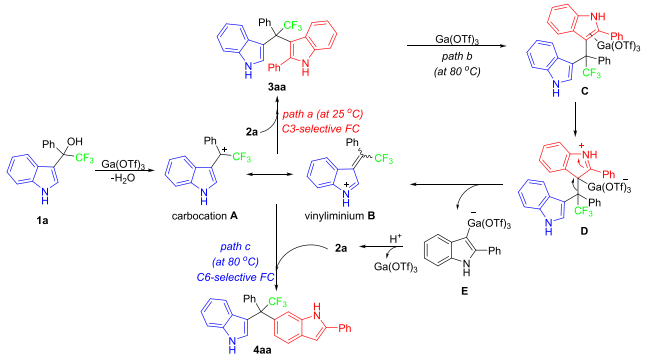
Scheme 5. Proposed Reaction Mechanism



$Ga(OTf)_3$, followed by elimination to generate the carbocation species **A** or its stabilized vinyliminium ion species **B**, which subsequently undergoes C3-selective Friedel−Crafts reaction with **2a** to deliver the 3,3′-BIM **3aa** (at room temperature, path a). However, under heating conditions, the steric crowding 3,3′-BIM **3aa** would be selectively activated by $Ga(OTf)_3$ due to the more electron-rich nature of 2-phenylindole moiety to yield the intermediate **D** via **C**, followed by C−C bond cleavage to reform the intermediate **A** or **B** and organogallium species **E**, which releases the catalyst by protodemetalation and produces 2-phenylindole **2a** (path b). An alternative pathway involving a direct C6-selective attack by **2a** from the intermediate **A** or **B** to furnish **4aa** without going through the intermediacy of **3aa** also could not be ruled out when the reaction was performed at 80 °C (path c). It is noteworthy that the C−C bond activation and fragmentation of triarylmethanes catalyzed by Lewis acids or Brønsted acids has been demonstrated in several reports.[20]

In summary, we have developed a novel and efficient protocol for the construction of unsymmetrical 3,3′- and 3,6′-bis(indolyl)methanes with a CF_3-containing all-carbon quaternary center via $Ga(OTf)_3$-catalyzed, temperature-dependent regioselective Friedel−Crafts alkylation reaction of trifluoromethylated 3-indolylmethanols with 2-substituted indoles. Unsymmetrical 3,3′- and 3,6′-BIMs can be selectively achieved by simply controlling the reaction temperature. In addition, this present protocol could be successfully extended to the synthesis of diverse difluoromethylated 3,3′- and 3,6′-BIMs with excellent efficiency. To the best of our knowledge, the conversion of 3,3′-BIMs to 3,6′-BIMs has been successfully realized for the first time in the present protocol.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01135.

Experimental procedure and spectroscopic data for all new compounds (PDF)

Accession Codes

CCDC 1904294 and 1904298 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge 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, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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