One-pot sequential synthesis of unsymmetrical diarylmethanes using methylene chloride as a C_1-synthon

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ABSTRACT

Bisindolylmethane (BIM) and its derivatives are widely used in the pharmaceutical industry due to their significant biological activities. However, most reported synthetic methods are focused on the synthesis of symmetric BIMs, while the synthesis of unsymmetrical BIMs remains a challenge. Herein, an unprecedented two-step one-pot method to afford unsymmetrically substituted 3,3′-BIM frameworks, using methylene chloride (DCM) as the C1-synthon is reported. In this protocol, the formation of two C–C bonds can be achieved *via* a one-pot reaction. The utility of commercially available phenols and anilines was also demonstrated in the construction of unsymmetrical diarylmethanes. This protocol provides a straightforward approach to access diverse unsymmetrical diarylmethane derivatives under simple and mild conditions. The broad substrate compatibility and good functional group tolerance of the protocol support its practical application potential.

INTRODUCTION

Diarylmethanes (DAMs) have attracted much attention due to their distinctive structural, chemical and physical properties. The DAM scaffold is a prevalent structural motif found in numerous biological natural products, synthetic compounds and functional materials.[1] 3,3′-Bisindolylmethanes (BIMs), characterized by two indoles linked to a single carbon at the 3- and 3′-positions, are considered "star molecules" within the diarylmethane family and are widely found in various bioactive natural products (Fig. 1).[2] These compounds exhibit diverse biological activities, such as antibacterial,[3] antifungal,[4] anti-leishmanial,[5] and antitumor[6] activities. In addition, synthetic BIMs are also known for their potential as dyes and some are even utilized as dietary supplements in our daily lives.[7,8] Moreover, BIMs are important building blocks in materials chemistry.[9] These highly desirable attributes have spurred significant interest in the development of efficient and ecofriendly synthetic methodologies to access this privileged structure.[2]

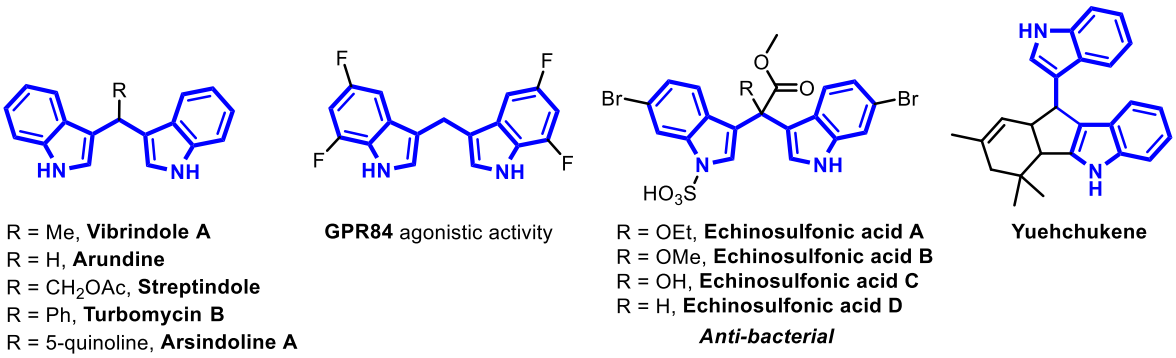
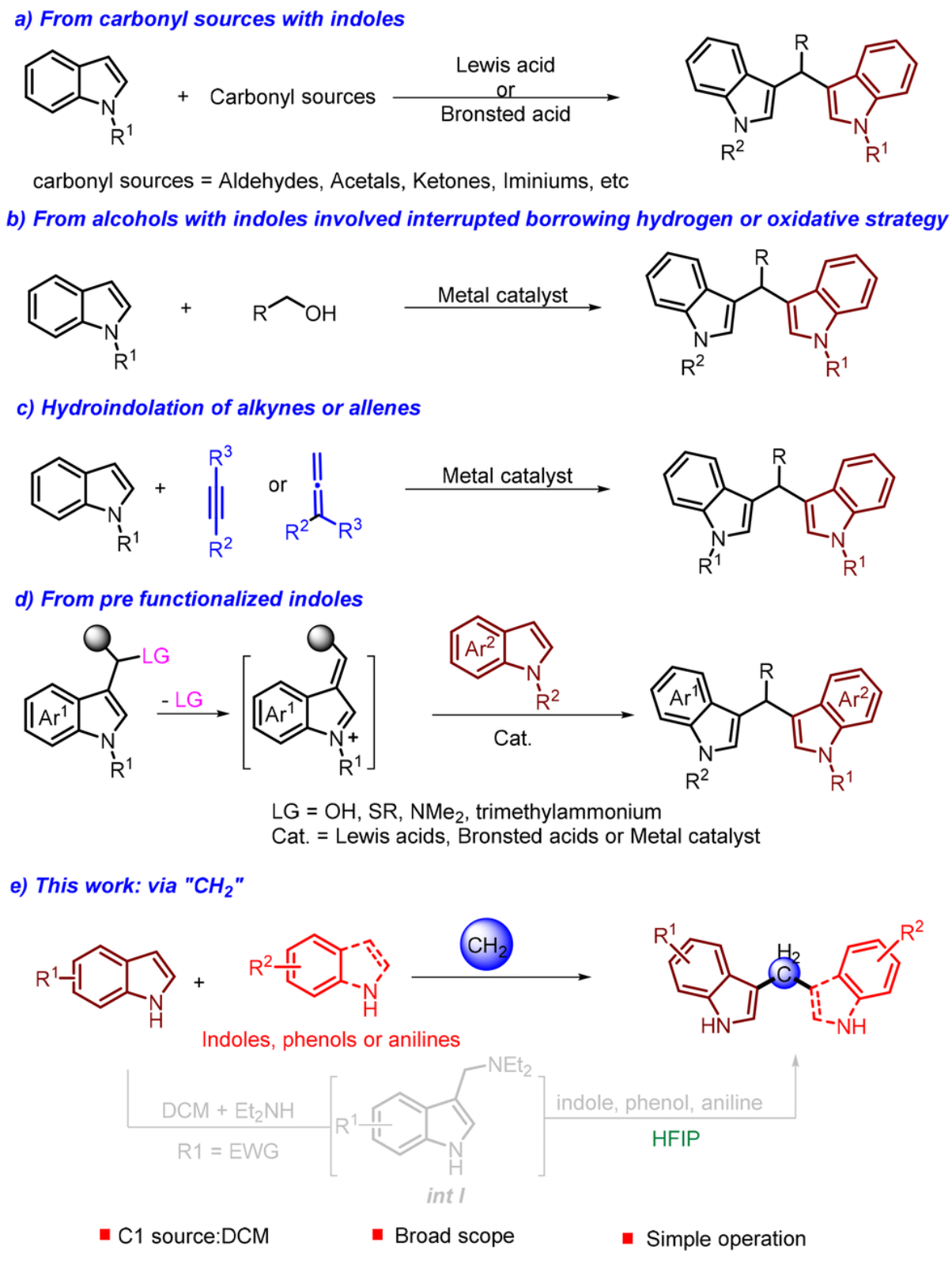


Figure 1. Representative bioactive 3,3′-BIMs.

Recently, numerous types of BIMs have been synthesized.[2] The well-established and practical synthetic methods for directly obtaining methylene bridged BIMs and their derivatives mainly rely on the condensation of indoles with carbonyl compounds or their precursors, as well as their related compounds *via* the double Friedel–Crafts pathway (Scheme 1a).[2,11–13] Another powerful alternative

method is to use C1-synthons, such as DMF, DMSO, TMEDA, HMTA, DMEA or TMU, as corrosive methylene sources to prepare 3,3′-bisindolylmethanes.[10,14] Primary alcohols have also been used for the construction of BIMs and their derivatives *via* a transition metal-catalyzed interrupted hydrogen borrowing strategy,[15] an Fe(ii)-catalyzed oxidation[16] strategy or electrochemically mediated synthesis methods[17] (Scheme 1b). Catalytic hydroindolation using alkynes[18] or allenes[19] as available substrates has been proved to be a powerful atom-economic approach for bis(indolyl)-alkane synthesis (Scheme 1c). Nowadays, advancements have also been made in photocatalytic reactions to afford BIMs and their derivatives.[20] However, most of these methods do not represent viable procedures for coupling two different indoles owing to the formation of symmetrical 3,3′-BIMs. Recently, attempts for the construction of unsymmetrical 3,3′-BIMs have been reported.[21] The most commonly used approaches toward their synthesis are to use pre-functionalized indoles with a leaving group at the C3-position, such as indolylmethanols,[22] indolylmethanamine derivatives[23] and indolylmethanthio derivatives[24] (Scheme 1d) or to use pre-functionalized indoles with alkenyl substituents at the 3-position,[25] to couple with another indole. However, these protocols suffer from some drawbacks such as the need for multistep synthetic routes, environmentally unfriendly reaction conditions and limited product diversity. Therefore, the development of more efficient and practical methods that avoid multistep synthetic routes is highly desirable for the synthesis of unsymmetrical 3,3′-BIMs and even a wider range of diarylmethane derivatives from readily available substrates.

Scheme 1 Strategies for the synthesis of BIMs.



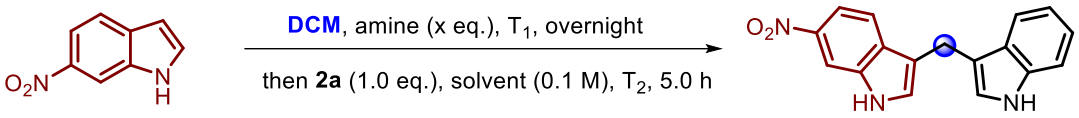
Based on our continuous interest in the exploration of indole derivative synthesis,[26] we herein disclose an unprecedented two-step one-pot method to afford unsymmetrically substituted 3,3′-BIM frameworks by using methylene chloride (DCM) as the C1-synthon to couple with 6-nitroindole and other indoles. Inspired by an elegant work that accessed unsymmetrical 3,3′-BIMs from indolylmethanamine derivatives,[23] we hypothesize that ((1*H*-indol-3-yl)methyl)ethanamine (*int I*) can be formed from a lower reactivity indole with dichloromethane and diethylamine *via* a Friedel–Crafts reaction in the first step. Then, *int I* undergoes the second Friedel–Crafts reaction with a higher reactivity indole in the magic solvent hexafluoroisopropanol (HFIP) to realize the synthesis of the unsymmetrical diindolylmethane without the isolation of the active intermediate ((1*H*-indol-3-yl)methyl)ethanamine (*int I*). In this protocol, the formation of two C–C bonds can be achieved with a one-pot sequential procedure (Scheme 1e). Meanwhile, we also synthesized unsymmetrical diarylmethane derivatives *via* a Friedel–Crafts reaction of 6-nitroindole with phenols or anilines using methylene chloride (DCM) as the C1-synthon.

RESULTS AND DISCUSSION

In this study, we selected 6-nitroindole (**1a**, 0.2 mmol) and indole (**2a**, 1.0 eq.) as the model substrates in the reaction. In the first attempt, the reaction was conducted in DCM (0.2 M) in a one-pot synthesis as proposed, and no desired product was formed. From previous literature,[23] we speculated that ((1*H*-indol-3-yl)methyl)ethanamine ***int I*** (Scheme 1e) could be a key intermediate, which coupled with another indole to construct BIMs. Then, a trial with diethylamine (Et_2NH) as a base was performed for the reaction. TLC monitoring showed that the reaction occurred but the reaction conditions resulted in relatively complex spots. Notably, the desired BIM (**3aa**) was indeed generated in the reaction in an

isolated yield of about 11%. The structure of **3aa** was elucidated by X-ray crystallography (CCDC 2258555†). We speculated that the above two indoles reacted without selectivity, and thus the reaction generated various BIMs and a number of intermediates of ((1*H*-indol-3-yl)methyl)ethanamines. Therefore, we conducted the reaction in a one-pot sequential manner. The reaction was first conducted overnight with 6-nitroindole **1a** and diethylamine (1.0 eq.) in dichloromethane. After that, the solvent was removed and replaced with HFIP, and the reaction was continued with the addition of indole **2a** at 80 °C (entry 1). The reaction yield (38%) was found to improve markedly. We then optimized the reaction with different amines under different loading, solvent, and temperature conditions (see the ESI† for details). As shown in Table 1, when diethylamine was replaced with other organic bases, the reaction gave no or low yields of **3aa** (entries 2–4). Notably, by increasing the amount of Et_2NH from 1.0 eq. to 3.0 eq., the yield increased from 38% to 54% (entries 1, 5 and 6). The reason for using excess Et_2NH was that the generated hydrogen chloride needed to be captured to improve the reaction yield. However, increasing the amount of Et_2NH to 4.0 eq. had no effect on the yield of **3aa** (entry 7). Solvent screening showed that HFIP was the best solvent (entries 6 and 8–12), probably due to the formation of hydrogen bonds between fluorinated alcohol solvents and intermediates, facilitating the second Friedel–Crafts reaction (entries 6 and 11).[27] Temperature screening showed that 90 °C for T_1 and 80 °C for T_2 was the most favorable (entries 6 and 13–18).

Table 1. Optimization of the reaction conditions



1a **3aa**

Entry	Amine (1.0 eq.)	T_1 [°C]	Solvent	T_2 [°C]	Yield (%)[b]
1	Et_2NH (1.0 eq.)	90	HFIP	80	38
2	Et_3N (1.0 eq.)	90	HFIP	80	10
3	Pyridine (1.0 eq.)	90	HFIP	80	ND [b]
4	Morpholine	90	HFIP	80	27
5	Et_2NH (2.0 eq.)	90	HFIP	80	49
6	Et_2NH (3.0 eq.)	90	HFIP	80	54
7	Et_2NH (4.0 eq.)	90	HFIP	80	55
8	Et_2NH (3.0 eq.)	90	DCM	80	10
9	Et_2NH (3.0 eq.)	90	MeOH	80	15
10	Et_2NH (3.0 eq.)	90	MeCN	80	ND [b]
11	Et_2NH (3.0 eq.)	90	TFE	80	40
12	Et_2NH (3.0 eq.)	90	THF	80	6
13	Et_2NH (3.0 eq.)	90	HFIP	60	18
14	Et_2NH (3.0 eq.)	90	HFIP	70	34
15	Et_2NH (3.0 eq.)	90	HFIP	90	41
16	Et2NH (3.0 eq.)	100	HFIP	80	42
17	Et2NH (3.0 eq.)	100	HFIP	100	48
18	Et2NH (3.0 eq.)	50	HFIP	80	18

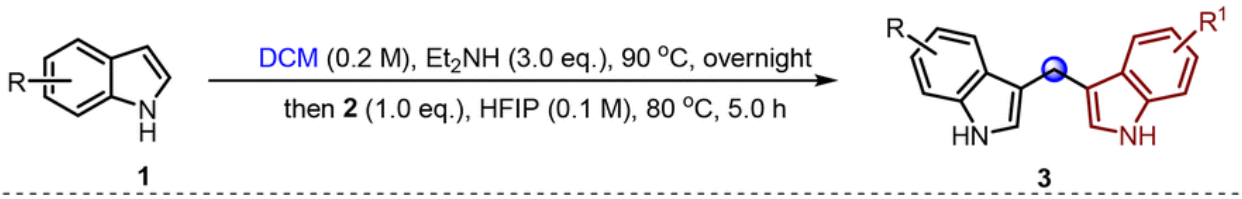
[a] **1a** (0.2 mmol), amine (*x* eq.), DCM (1.0 mL), 90 °C, overnight, then **2a** (0.2 mmol), T_2, solvent (2.0 mL), 5.0 h, isolated yield. [b] ND: not detected.

Under the optimized reaction conditions, the substrate scope of indoles with 6-nitroindole (**1a**) was investigated. As shown in Scheme 2, the reaction proceeded efficiently to form unsymmetrical 3,3′-BIMs. In general, regardless of the substitution position and the electronic properties of the substituent on indole **2**, the Friedel–Crafts reaction proceeded smoothly and gave the desired products in moderate to good yields (31–84%). A series of synthetically useful functional groups, such as methyl formate

(**3ad** and **3ar**), acetoxy (**3af**), methoxy (**3ag**), chloro (**3ap** and **3at**), bromo (**3aq**, **3av** and **3aw**), iodo (**3ai**), acetyl (**3aj**), formyl (**3ak**), or cyano (**3ar**), were found to be tolerated well in the reaction and the corresponding products were obtained in 38–84% yields. However, the substituents showed some steric effects on the reaction since C2- or/and C4-substitutions on indole **2** gave the desired products **3ac** and **3ae** in relatively low yields of 36% and 35%, respectively. The coupling partners **2** with di-substituents on the phenyl ring also participated in the reaction well, giving the corresponding products **3au** and **3av** in 82% and 67% yields, respectively.

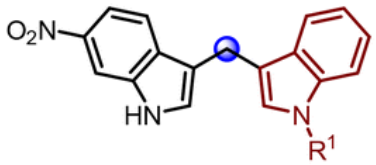
Next, we investigated the scope of the indole substrates **1**. However, it was found that not all indoles were able to form the key intermediate **int I** effectively, for example, unsubstituted indole or 7-methylindole generated a lot of impurities, as indicated by TLC monitoring during the first reaction step. Therefore, highly active indoles cannot be used to construct BIMs using this method. It was noteworthy that when the indole substrates bearing electron-withdrawing groups, such as 4-nitro (**1b**), 5-nitro (**1c**) *N*-methyl-5-nitro (**1d**), 7-nitro (**1e**), 7-chloro (**1f**), 6-methyl formate (**1g**) and 7-azaindole (**1h**), were used, the desired products (**3ba–3ha**) were obtained smoothly, although their yields were not high.

Scheme 2. Synthesis of Asymmetric 3,3'-DIMs from indoles

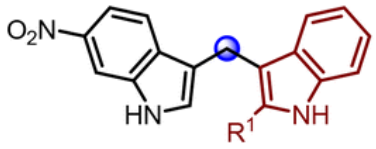


1 3

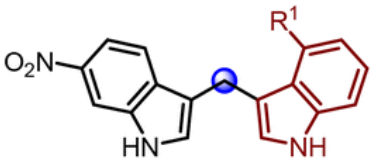
R = 6-NO$_2$



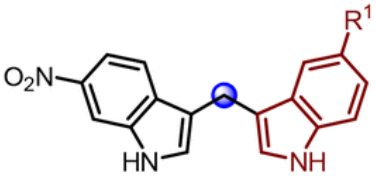
3aa R^1 = H, 54%
3ab R^1 = Me, 60%



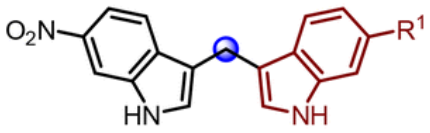
3ac R^1 = Me, 36%
3ad R^1 = COOMe, 51%



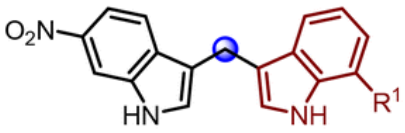
3ae R^1 = Me, 35%
3af R^1 = OAc, 49%



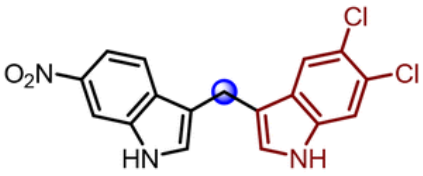
3ag R^1 = OMe, 60%
3ah R^1 = F, 57%
3ai R^1 = I, 59%
3aj R^1 = Ac, 68%
3ak R^1 = CHO, 72%



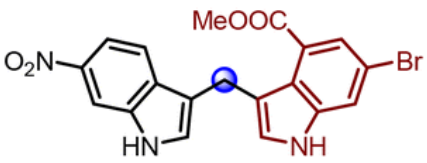
3al R^1 = Me, 53%
3am R^1 = OBn, 41%
3an R^1 = CF$_3$, 44%
3ao R^1 = F, 65%
3ap R^1 = Cl, 42%
3aq R^1 = Br, 64%
3ar R^1 = COOMe, 50%
3as R^1 = CN, 38%



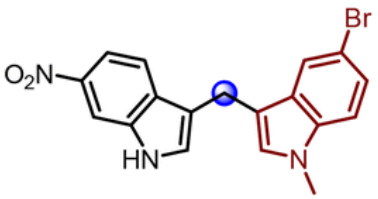
3at R^1 = Cl, 84%



3au 82%

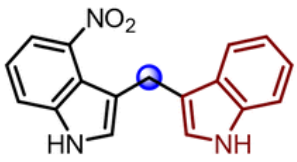


3av 67%

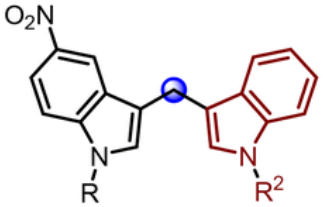


3aw 31%

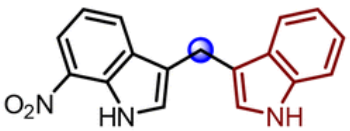
R^1 = H



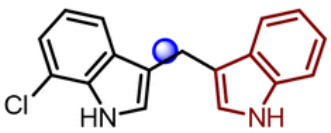
3ba 39%



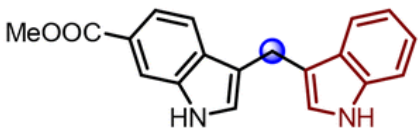
3ca R = R^2 = H, 19%
3da R = R^2 = Me, 50%



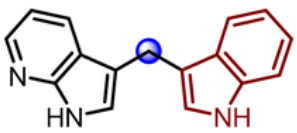
3ea 33%



3fa 37%



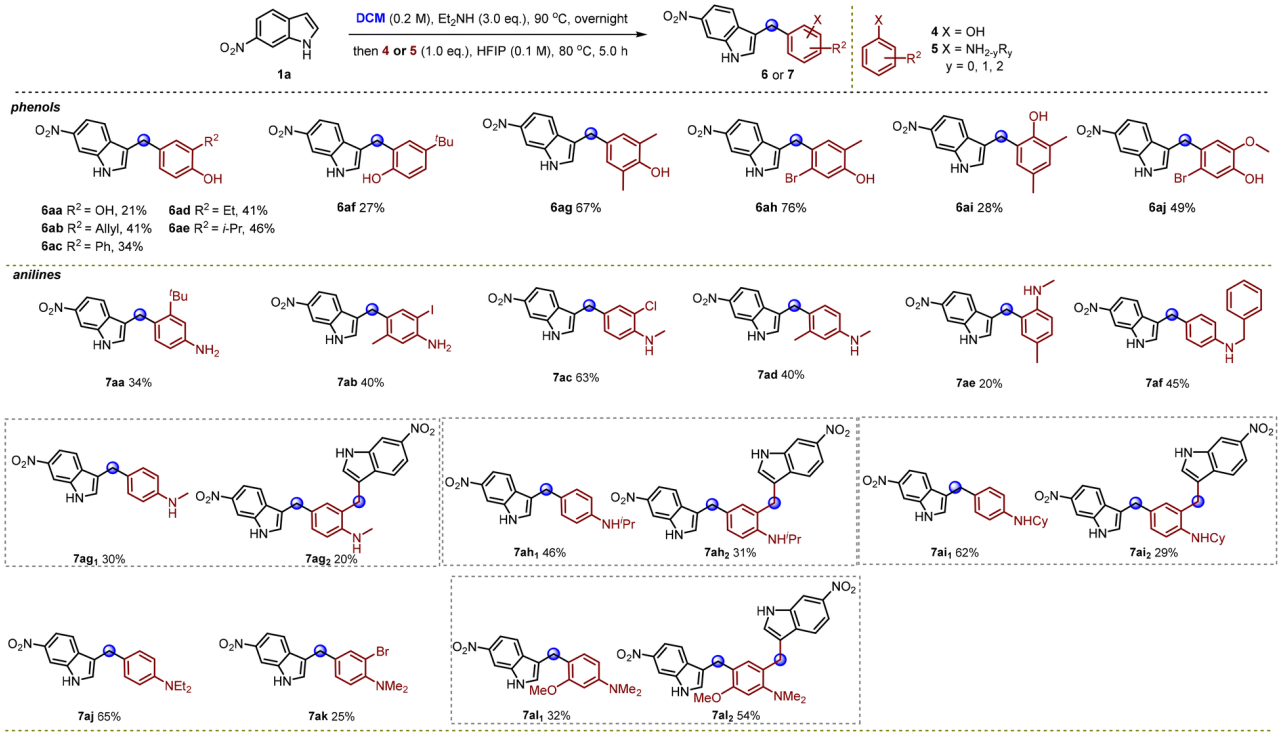
3ga 20%



3ha 47%

Subsequently, the scope of phenols was examined (Scheme 3). Using 6-nitroindole (**1a**) as the substrate, a series of phenols were found to be compatible with the reaction, in which the desired products (**6aa–6aj**) were obtained in 21–76% yields. In the case of 2-substituted phenols, the *para*-substituted products **6aa–6ae** and **6ag** were formed in moderate yields (21–67%), whereas using the 4-substituted phenols as a coupling partner, the *o*-substituted products **6af** and **6ai** were obtained in yields of 27% and 28%, respectively. The low yield of **6ae**, **6ai**, and **6af** may be due to the effect of steric hindrance, while the low yield of **6aa–6ad** was due to the occurrence of *ortho*-substitution. It is noteworthy that di-substituted phenols also reacted smoothly to give the products **6ag–6aj** in 28–76%, which showed the wide applicability of this protocol.

Scheme 3. Synthesis of Aryl methanes from phenols and anilines [a]



Furthermore, the reaction of 6-nitroindole with different anilines was studied. As shown in Scheme 3, the reaction generally gave 20–65% yields of the target products (**7aa–7al2**) when anilines are used as the coupling partners. When using *ortho*- or *meta*-substituted anilines as coupling reagents, irrespective of whether they were primary, secondary or tertiary-amines, only the *para*-substituted products (**7aa–7ae** and **7ak**) were afforded in majority of the cases in 20–63% yields; however, *N*,*N*-dimethylaniline with a strong electron-donating group (–OMe) at the C3-position was an exception. This reagent not only gave the *para*-substituted product (**7al1**) in 32% yield but also gave *ortho*, *para*-disubstituted product (**7al2**) with 54% yield. It is noteworthy that when using unsubstituted secondary anilines, both *p*-substituted and *ortho*, *para*-disubstituted products were obtained (**7ag–7ai**). It is worth noting that *N*-benzyl substituted aniline was an exception, as only the *para*-alkylated product **7af** was obtained.

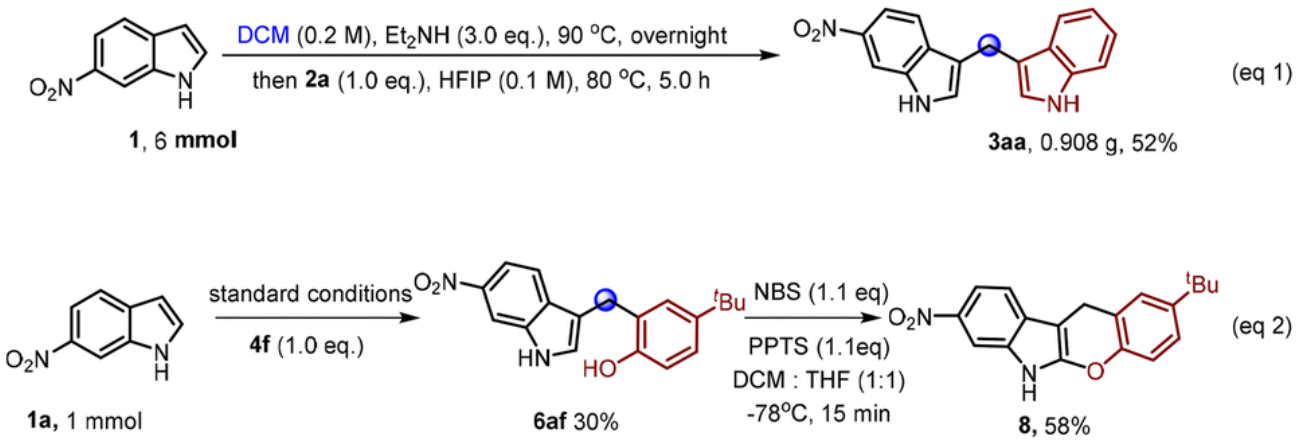
To demonstrate the practicality of the reaction, a gram-scale reaction of **1a** (3.5 mmol) with **2a** was performed. Similarly, product **3aa** was isolated in 52% (Scheme 4, eqn (1)). Then the coupling of **1a** with **4f** was conducted at the 1 mmol scale to give **6af** in 30% yield, the yield of which was slightly higher than that at the 0.2 mmol scale. The derivation of **6af** was demonstrated by using NIS as an oxidant to give the cyclization product **8** in 58% yield (Scheme 4, eqn (2)).

To elucidate the mechanism of this transformation, control experiments were performed (Scheme 5). First, radical inhibition experiment was conducted by using BHT (1.0 eq.) as the radical inhibitor. The result showed irrrespective of whether BHT was added in the first or second step (eqn (1)), it had no effect on the yield of **3aa**, showing that this transformation was unlikely to take place *via* a radical process. Next, when using the strong electrophilic benzal chloride as the reactant, symmetric 3,3′-

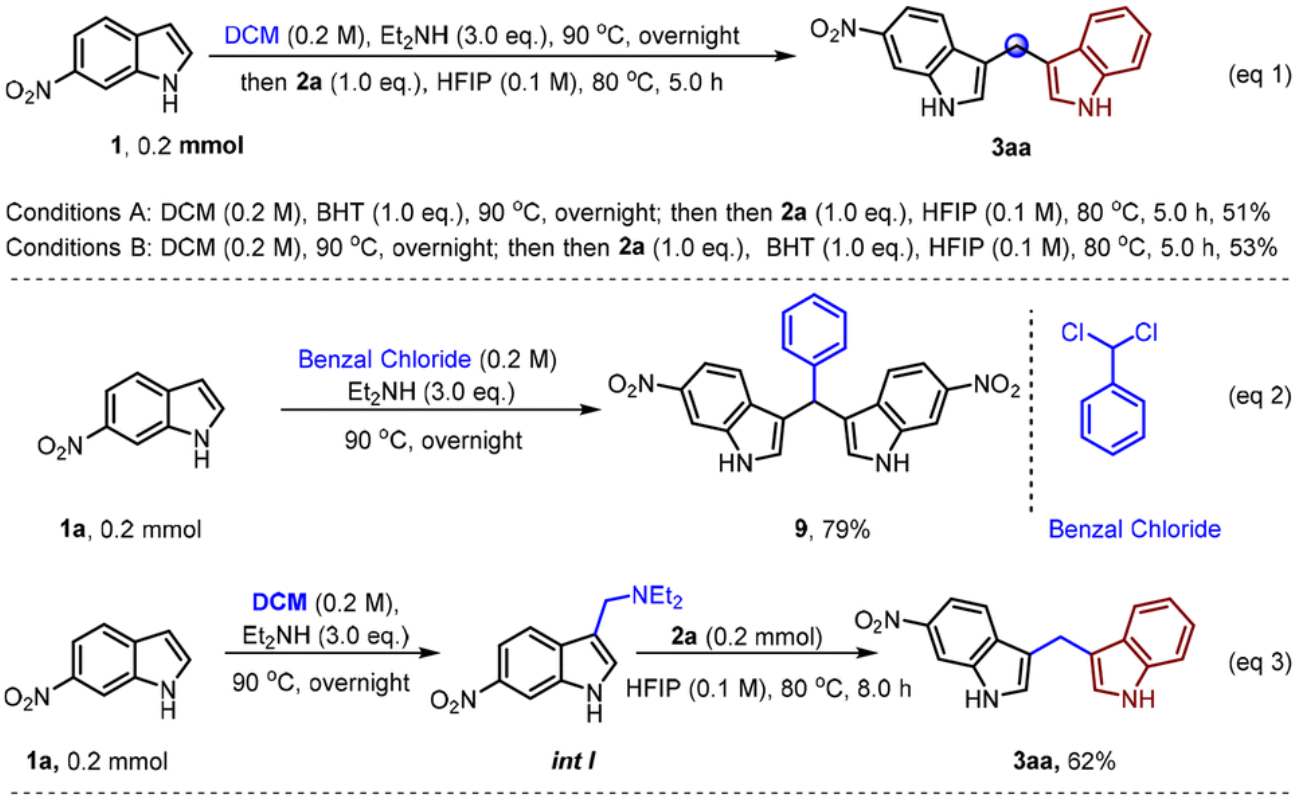
(phenylmethylene)bis(6-nitro-1*H*-indole) **9** was obtained in the presence of diethylamine (eqn (2)). This result indicates that using DCM as a C1 synthon to construct BIMs may involve the formation of **int I**. To gain further mechanistic insights into this protocol, we tried to capture the reaction intermediate **int I**. After the reaction between 6-nitroindole and diethylamino in dichloromethane, a large amount of solid was precipitated, which was confirmed using ^{1}H NMR to be the proposed **int I**. Further reaction of **int I** with indole under the standard conditions afforded 62% yield of product **3aa** (eqn (3)). These results further confirm that the reaction involves the production of intermediate **int I** in the first step of Friedel Crafts reaction.

Based on these experimental results and previous reports,[20] a plausible mechanism was proposed, as illustrated in Scheme 6. Initially, diethylamine underwent an S_N2 reaction with dichloromethane to form an *N*-chloromethyl-*N*-diethylamine intermediate, where dichloromethane was a C1 synthon. After that, the intermediate underwent Friedel–Crafts reaction at the C3-position of 6-nitroindole to form **int I**, which subsequently underwent another S_N2 reaction, facilitated by fluorinated alcohol solvents, with indoles or phenols or anilines to form the target products. A diethylamine was released into the reaction cycle (Scheme 5).

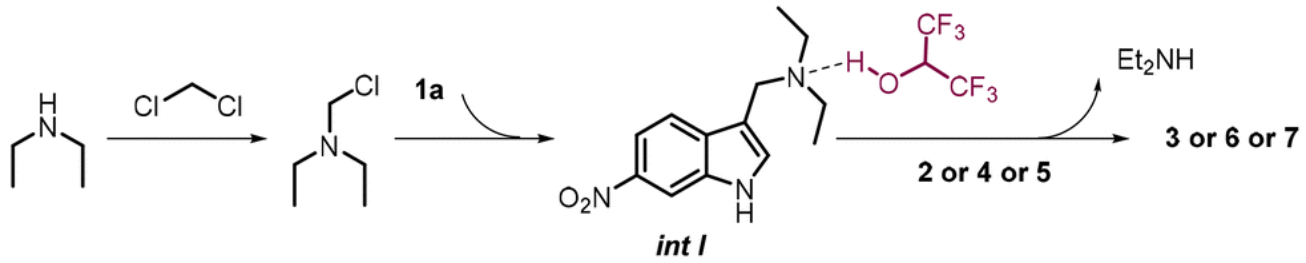
Scheme 4. Gram-scale synthesis of 3aa and derivation of 6af.



Scheme 5. Mechanistic studies.



Scheme 6. Proposed Mechanism



CONCLUSIONS

An efficient Friedel–Crafts reaction of 6-nitroindole with indoles, phenols or anilines by using dichloromethane as a C1 synthon was developed. This protocol provides access to a series of unsymmetrical 3,3′-bisindolylmethanes and diarylmethane derivatives. The protocol is achieved by using dichloromethane as a methylene precursor, with excellent atom and step economy. In addition, simple starting materials, no toxic by-products and simple reaction conditions make this method highly practical and eco-friendly.

Author contributions

J. H., W.-L. W., and J.-Q. W. conceived the idea and designed the research. X. C., C. C., M. X., T. Z., J. Y., W. S. and Z. X. performed the research. X. C. analyzed the data. J.-Q. W. wrote the original manuscript. W.-L. W. and J. H. reviewed the manuscript and suggested improvements.

Data availability

The authors confirm that the data supporting the findings of this study are available within its ESI.†

Conflicts of interest

There are no conflicts to declare.

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