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Triphenylphosphine-*m*-sulfonate/Carbon Tetrabromide as an Efficient and Easily Recoverable Catalyst System for Friedel–Crafts Alkylation of Indoles with Carbonyl Compounds or Acetals

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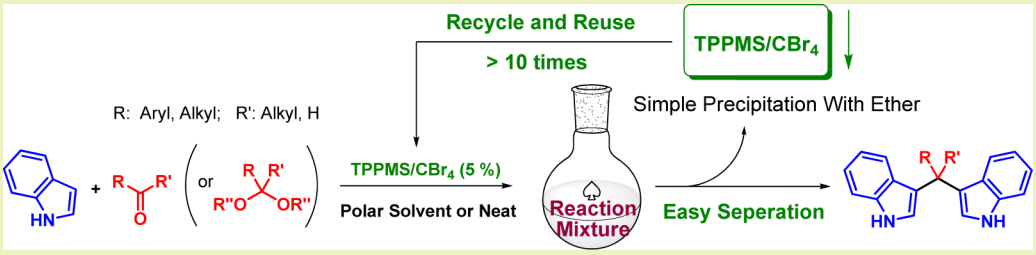
Supporting Information



ABSTRACT: A solid complex, conveniently prepared from commercially available sodium triphenylphosphine-*m*-sulfonate (TPPMS) and carbon tetrabromide, can be used as an easily recoverable and reusable catalyst system for Friedel–Crafts alkylation of indoles with carbonyl compounds or acetals to produce bis(indolyl)alkane products (BIAs).

KEYWORDS: *Friedel–Crafts alkylation, Indoles, Carbonyl compounds, Recoverable catalyst*

INTRODUCTION

Friedel–Crafts (FC) reaction is one of the cornerstone reactions for carbon–carbon bond construction and has been widely used to generate important classes of building blocks.[1−10] However, the methods often suffer from drastic reaction conditions and more than stoichiometric amounts of catalysts. With the recent increased environmental and economic awareness, the development of greener and/or sustainable methods for this fundamental transformation has emerged in recent years.[5−10]

3,3′-Bis(indolyl)alkanes (BIAs) were widely isolated from various terrestrial and marine natural sources, which exhibit a range of important biological activities.[11] Therefore, there is a great deal of interest in the synthesis of this class of compounds since it was first prepared by Fischer in 1886.[12] The practical synthetic method of this skeleton is the FC reaction between indoles and carbonyl compounds, which generally require a stoichiometric amount of the Lewis acids or Brönsted acid. Therefore, the development of green methods to construct BIAs is still highly desired.[13−15]

Sodium triphenylphosphine-*m*-sulfonate (TPPMS) is a commercially available reagent that is used industrially as a ligand for the Rh-catalyzed biphasic hydroformylation reactions.[16,17] Recently, we demonstrated that TPPMS can be used as an ion-tagged reagent to mediate a facilitate Wittig reaction.[18] The product alkenes were often sufficiently pure without chromatographic purification. Shortly afterward, we developed the use of the TPPMS/CBr_4 complex as a highly efficient catalyst for the preparation of acetals from aldehydes and for the tetrahydropyranylation of alcohols.[19] In these reactions, as a solid complex, the TPPMS/CBr_4 system is stable and can be kept readily. The catalyst is soluble in relatively polar organic solvents such as methanol but can be easily and quantitatively recovered from the reaction mixture by simply adding a nonpolar organic solvent such as ether. The recovered catalyst can be reused without loss of catalytic activity.

As part of our ongoing program to develop highly efficient and environmentally benign synthetic processes, we are interested in exploring new catalytic activities for this solubility controllable TPPMS/CBr_4 complex. Herein, an efficient FC reaction of indoles with carbonyl compounds or acetals catalyzed by TPPMS/CBr_4 complex to achieve various BIAs is introduced in this paper.

RESULTS AND DISCUSSION

The TPPMS/CBr_4 complex used in this study was produced as follows. A mixture of TPPMS and carbon tetrabromide (1:1 molar ratio) was stirred at room temperature in methanol for 4 h, and then the reaction mixture was concentrated and ether was added to precipitate the TPPMS/CBr_4 complex as a white solid.

Our investigations started with the reaction between *p*-chlorobenzaldehyde (2i) and indole (1) (Table 1). The solvents are crucial to the reaction, and the best result was

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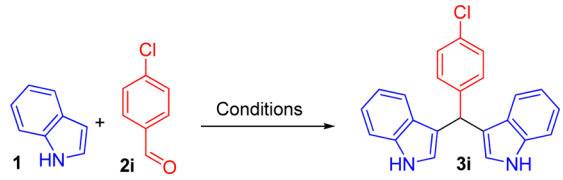
Table 1. Reaction Conditions Optimization

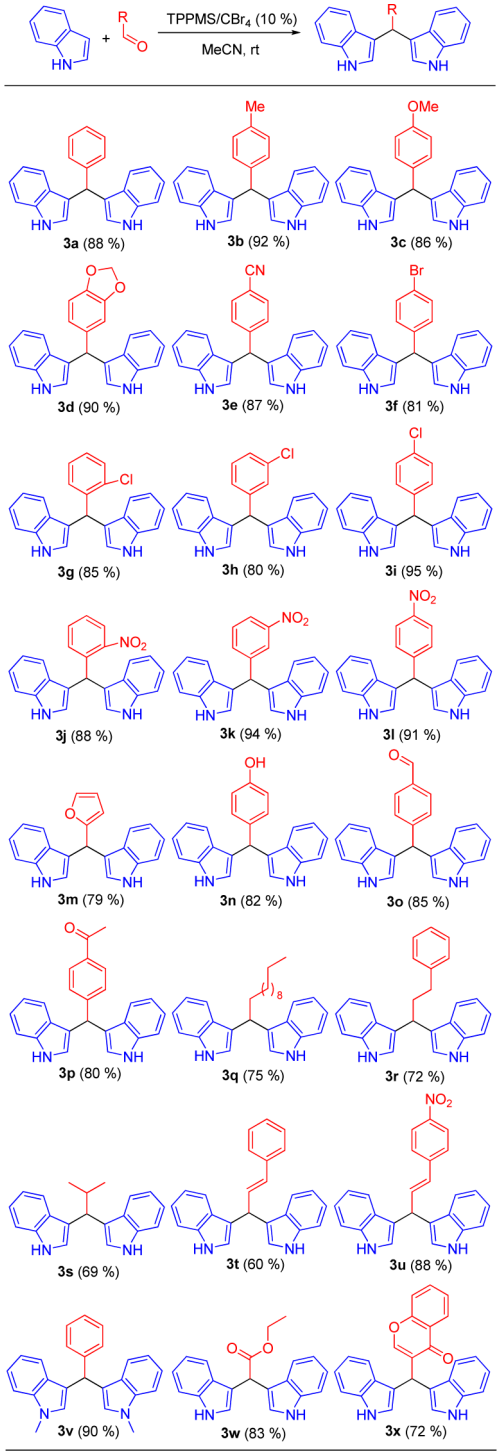


entry	conditions	NMR yield of 3i (%)
1	10% TPPMS/CBr_4, **MeCN**, rt, 4 h	95
2	**10%** TPPMS/CBr_4, **DCM**, rt, 4 h	75
3	**10%** TPPMS/CBr_4, **THF**, rt, 4 h	37
4	10% TPPMS/CBr_4, **Dioxane**, rt, 4 h	30
5	10% TPPMS/CBr_4, **EtOAc**, rt, 4 h	44
6	10% TPPMS/CBr_4, **Acetone**, rt, 4 h	58
7	**1%** TPPMS/CBr_4, MeCN, rt, 4 h	51
8	**2%** TPPMS/CBr_4, MeCN, rt, 4 h	84
9	**5%** TPPMS/CBr_4, MeCN, rt, 4 h	93
10	10% **TPPMS**, MeCN, rt, 4 h	-
11	10% **CBr_4**, MeCN, rt, 4 h	-

obtained by the use of CH_3CN as solvent. Encouraged by the initial results, we went on to investigate the generality of this procedure. We examined the reactivity of various aldehydes as summarized in Table 2. In general, the TPPMS/CBr_4 complex was able to catalyze the FC reaction of both aryl and aliphatic aldehydes with indole. The reaction conditions are usually quite mild, simply stirring of the solution at room temperature. Aryl aldehydes with electron-donating substituents and with electron-withdrawing substituents were all well tolerant of the reaction conditions (Table 2, 3a−3p). The aldehydes with *ortho* or *meta* substituents delivered the corresponding alkylated indoles in high yields (Table 2, 3g, 3h, 3j, 3k), illustrating that steric hindrance played a poor role to the reaction. The procedure was also successfully applied for heteroaromatic aldehydes (Table 2, 3m), and their corresponding BIAs were obtained at high yields. The reaction was tolerant of unprotected phenols (Table 2, 3n) with the adduct of 4-hydroxybenzaldehyde being isolated in 82% yield. Aliphatic aldehydes also gave good yields of the corresponding BIAs (Table 2, 3q−3s). Furthermore, the reaction of indole with cinammaldehydes (Table 2, 3t, 3u) as α,β-unsaturated aldehydes furnished moderate to excellent yields of the corresponding BIAs. The N-substituted indole presented equally high efficiency in respect to that of free indole to give the adduct in high yields (Table 2, 3v). Ethyl bis-1H-indol-3-yl-acetate, 3w, as the important intermediate for the synthesis of pharmacologically interesting natural product Streptindole,[20−23] was prepared by our method in 83% yield, and biologically interesting (chromon-3-yl)bis(indol-3-yl)-methanes[24,25] 3X was also prepared in high yield. The ketones failed to furnish the BIAs under the reaction conditions and were recovered quantitatively. 4-Acetylbenzaldehyde reacted with indole to give the BIA 3p in good yield, demonstrating high chemoselectivity.

In the reaction, the separation and recovery of the catalyst system was simply carried out by precipitation with ether after completion of the reaction. The recovered catalyst can be reused without loss of catalytic activity. We demonstrated this with the FC reaction of *p*-chlorobenzaldehyde with indole using recovered TPPMS/CBr_4 system for 10 cycles without distinctly diminished yield (Figure 1.).

Table 2. TPPMS/CBr_4 Catalyzed FC Alkylation Reactions of Indole with Aldehydes (isolated yields in parentheses)



Cyclic arenecarbaldehyde acetals have previously found use in Friedel−Crafts reactions, which proceed to give the alkylated products in high overall yield.[26,27] The reaction catalyzed by the TPPMS/CBr_4 complex between indole and acetals were next investigated. We were gratified to observe that reactions of indole with acetals in acetonitrile gave efficient conversions to the desired products. In all cases, the reaction of dimethyl acetals derived from aldehydes provided the bisindolylalkane product in excellent yield in short reaction times (Table 3,

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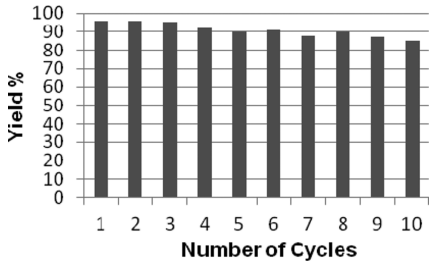
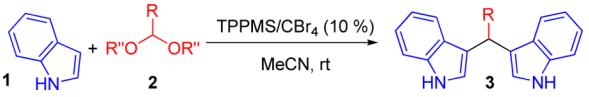
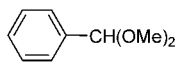
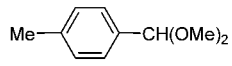
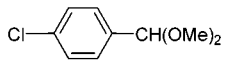
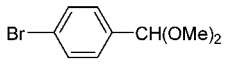
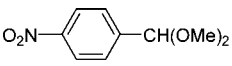
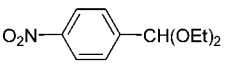
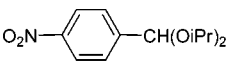
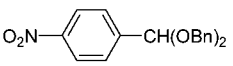
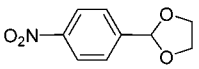


Figure 1. Studying reusablility of TPPMS/CBr_4 in the reaction of *p*-chlorobenzaldehyde with indole.

entries 1–5). Reactions involving other acetals (Table 3, entries 6–9) also proceeded efficiently, giving excellent isolated yields.

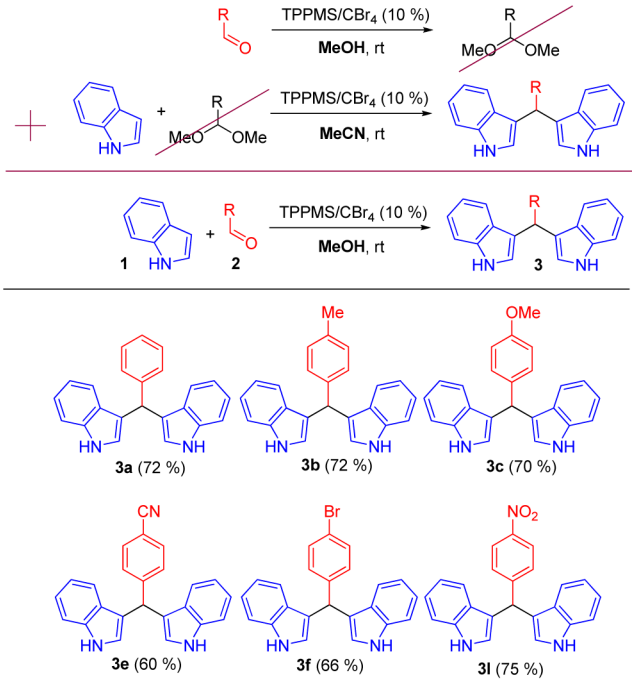
Table 3. TPPMS/CBr_4 Catalyzed FC Alkylation Reactions of Indole with Acetals



Entry	2	Time	3 Yield %
1			75
2			77
3			74
4			72
5			85
6			82
7			80
8			51
9			63

Furthermore, Graham et al. reported last year on a nanoporous aluminosilicate catalyzed tandem acetalization–FC protocol in which the acetal is generated in situ and undergoes subsequent FC reaction.[28] The main benefit of this protocol is allowable of using environmentally preferable solvents, such as methanol. We have previously demonstrated that the TPPMS/CBr_4 complex is a highly efficient catalyst for the direct conversion of aldehydes to acetals in the presence of alcohols and diols without the requirement for additional dehydrating agents.[19] As an extension of this chemistry, we envisioned that the TPPMS/CBr_4 complex might also be utilized to promote the tandem acetalization–FC reaction of aldehydes and indoles in simple alcohols. It was expected that after the acetalization of aldehydes, the acetals generated in situ would undergo the FC alkylation to produce BIAs. We investigated the reaction between indole and a few aldehydes in methanol as shown in Table 4. The reaction performed smoothly, but not as effectively as the same reaction in acetonitrile.

Table 4. TPPMS/CBr_4 catalyzed FC alkylation reactions in methol (isolated yields in parentheses)



There is an increasing interest in solvent-free reactions. This protocol leads to a clean, efficient, and economical technology not only with the increment of safety, the simpleness of work up, and the reduction of cost, but also increased amounts of reactants can be achieved in the same equipment without huge modifications.[29−32] We then proceed to examine our method under solvent-free conditions. We got very exciting results that beside aldehydes, both aromatic and aliphatic ketones were also transformed to the desired BIAs with good to excellent yield. The ketones' reactivity may be enhanced due to without dilution in solvent-free condition. The results are shown in Table 5.

To evaluate the practicability of our method,[33,34] the reaction between indole (1) and *p*-chlorobenzaldehyde (2i) has been performed on a large scale [11.6 g 1 (100 mmol) + 7 g 2i (50 mmol)] in a single batch, and to our delight, no yield loss was observed with even lower initiator loading (5 mol % TPPMS/CBr_4 in 25 mL MeCN at room temperature, finished in 4 h, 97% isolated yield). That is to say, here we present a practical and scalable synthetic entry to the BIA derivatives.

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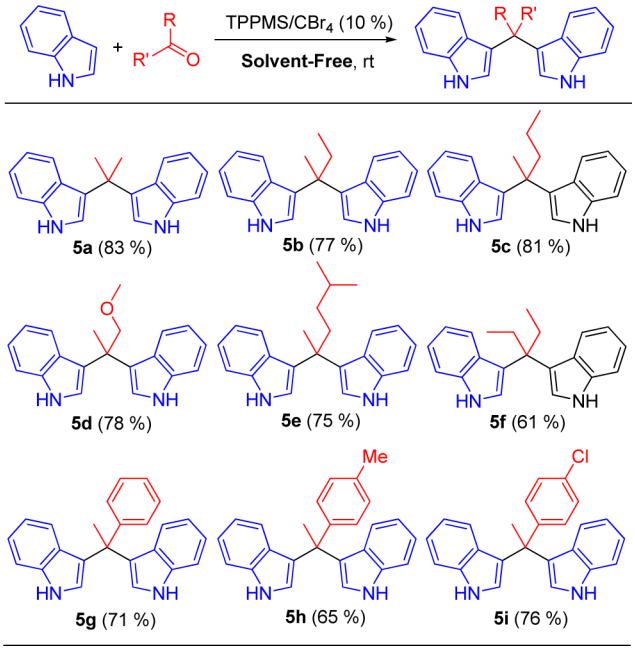
Table 5. TPPMS/CBr_4 Ctalyzed FC Alkylation Reactions of indole with Ketones (isolated yields in parentheses)



EXPERIMENTAL SECTION

Typical procedure for TPPMS/CBr_4 catalyzed FC alkylation reactions of indole with aldehydes follows. Indole (1, 2 mmol) and the appropriate aldehyde (2, 1 mmol) were dissolved in MeCN (1 mL) at ambient temperature. THe TPPMS/CBr_4 complex (10 mol %) was then added under stirring. The reaction completed within 2−8 h as monitored by TLC. Ether (5 mL) was added, and the solid TPPMS/CBr_4 complex was recovered by filtration. The liquid filtrate was evaporated to give the corresponding BIA products. Further purification by recrystallization or flash chromatography may be required in some cases.

Typical procedure for TPPMS/CBr_4 catalyzed FC alkylation reactions of indole with acetals follows. Indole (1, 2 mmol) and the appropriate acetal (2, 1 mmol) were dissolved in MeCN (1 mL) at ambient temperature. The TPPMS/CBr_4 complex (10 mol %) was then added under stirring. The reaction completed within 2−6 h as monitored by TLC. Ether (5 mL) was added, and the solid TPPMS/CBr_4 complex was recovered by filtration. The liquid filtrate was evaporated and purified to give the corresponding BIA products.

Typical procedure for TPPMS/CBr_4 catalyzed FC alkylation reactions of indole with ketones follows. Indole (1, 2 mmol) and the appropriate ketone (2, 5 mmol, excess) were mixed together at ambient temperature. The TPPMS/CBr_4 complex (10 mol %) was then added under stirring. The reaction completed within 8−12 h as monitored by TLC. Ether (5 mL) was added, and the solid TPPMS/CBr_4 complex was recovered by filtration. The liquid filtrate was evaporated and purified to give the corresponding BIA products.

CONCLUSION

In conclusion, we have demonstrated that the TPPMS/CBr_4 complex is a highly efficient catalyst for the synthesis of 3,3′-bis(indolyl)alkanes from a range of aldehydes, ketones, and acetals in high yields. The synthesis proceeds at room temperature without the requirement of inert or anhydrous reaction conditions. The catalyst is stable and can be kept readily. It is easily separable from the substrate and product and can be recovered and reused without loss of catalytic activity for 10 cycles.

ASSOCIATED CONTENT

Supporting Information

Copies of ^1H NMR and ^{13}C NMR. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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