Brønsted Acid Catalyzed Synthesis of Unsymmetrical Arylbis(3-indolyl)methanes

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Abstract: Unsymmetrical arylbis(3-indolyl)methanes have been synthesized via a Brønsted acid catalyzed Friedel–Crafts alkylation of α-(3-indolyl)benzylamines with *N*-methylindole. With 5 mol% of the catalyst, the reaction proceeds smoothly under mild conditions, affording the unsymmetrical triarylmethanes in excellent yields (up to 98%).

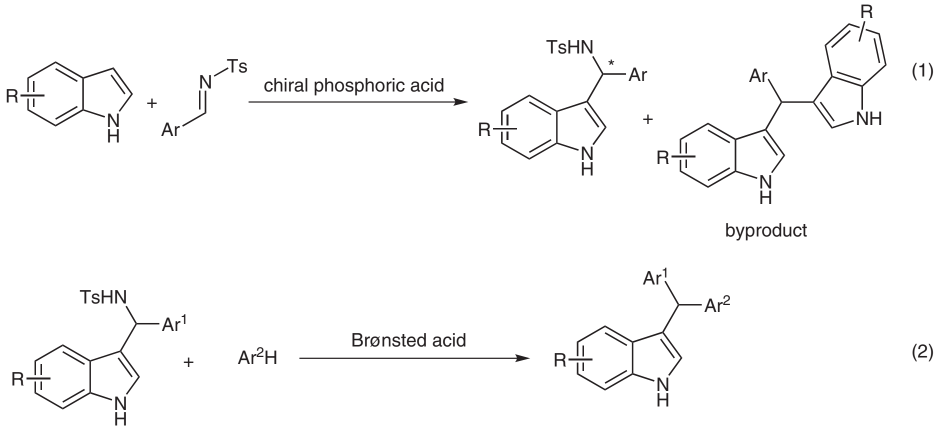
Key words: Brønsted acids, Friedel–Crafts reaction, indole, unsymmetrical triarylmethane

The synthesis of triarylmethanes has attracted enormous attention from synthetic community due to their versatile applications such as biologically active compounds, protecting groups in organic synthesis, and important dyes.[1] Unsymmetrical arylbis(3-indolyl)methanes in particular have attracted considerable synthetic interests. There have been many reports recently on the synthesis of arylbis(3-indolyl)methanes.[2] However, most of the current efforts have been made towards the synthesis of symmetrical arylbis(3-indolyl)methanes,[3] the synthesis of unsymmetrical triarylmethanes remains challenging and less explored.[4]

During our recent study on the chiral phosphoric acid catalyzed Friedel–Crafts reaction of indole, we observed that a side reaction occurred to afford arylbis(3-indolyl)methane byproducts (Scheme 1, equation 1).[5,6] Given the great importance of the indole-containing triarylmethanes[7] and the challenge for the synthesis of unsymmetrical triarylmethanes, we envisaged that the synthesis of unsymmetrical triarylmethanes might be realized through the Brønsted acid catalyzed Friedel–Crafts alkylation of α-(3-indolyl)benzylamine with another electron-rich arene (Scheme 1, equation 2). In this paper, we report a Friedel–Crafts-type reaction of α-(3-indolyl)benzylamine with *N*-methylindole, and the unsymmetrical arylbis(3-indolyl)methanes could be obtained in up to 98% yield.

We first examined the reaction between α-(3-indolyl)benzylamine with *N*-methylindole catalyzed by a readily available achiral Brønsted acid **1**, developed originally by Terada and coworkers.[8] With 5 mol% of **1** as catalyst, various solvents were examined for their effectiveness (Table 1). Both dichloromethane and diethyl ether could be used for the reaction except that a longer reaction time (24 h) was needed in the latter case. The reaction in THF was slow and gave products in lower yields. Toluene was found to be the optimal solvent, and the reaction proceeded to completion within 1 hour at room temperature, affording the desired product **4a** in 94% yield.[9,10] The reaction also worked with H_3PO_4, TFA, and TsOH·H_2O, but in lower yields (entries 5–7, Table 1).

In the presence of 5 mol% of **1**, the reaction of various α-(3-indolyl)benzylamine derivatives with *N*-methylindole were evaluated to examine the generality of the reac-



Scheme 1 Synthesis of unsymmetrical triarylmethanes inspired by a side reaction

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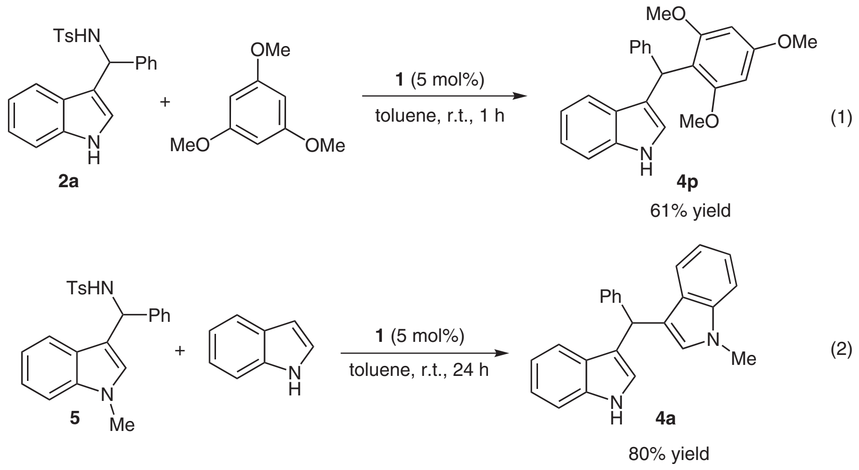

Scheme 2 Examination of the substrate scope

tion. The results are summarized in Table 2. For the substituents on the aryl group of **2**, electron-donating groups (**2b**,**c**) accelerated the reaction, whereas reactions with electron-withdrawing groups (**2d**–**g**) were relatively slow. Fortunately, excellent yields were obtained in both cases (83–97% yield, entries 1–7, Table 2). Substituents at the different positions of indole (**2h**–**n**) with different electronic properties did not show any notable effects on the reaction rate. In all cases, moderate to excellent yields were obtained (66–98% yield, entries 8–14, Table 2). Interestingly, excellent yield (88%) was obtained even in the case of 2-methyl substituted indole **2o** (entry 15, Table 2).

In addition to *N*-methylindole, the current catalytic system also worked for 1,3,5-trimethoxybenzene, providing the unsymmetrical triarylmethane **4p** in 61% yield (Scheme 2, equation 1). It should be pointed out that no reaction occurred when α-(3-indolyl)benzylamine **2a** was replaced by the simple *N*-diarylmethyltosylamide. However, the reaction between **5** and indole in the presence of 5 mol% **1** still proceeded to afford **4a** in 80% yield in a much longer reaction time (24 h; Scheme 2, equation 2).

Mechanistically, we proposed the following catalytic cycle as listed in Scheme 3. With the assistance by Brønsted acid (X–H), α-(3-indolyl)benzylamine **2a** undergoes elimination of amine moiety to afford the intermediate **I**. Intermediate **I** reacts with *N*-methylindole via a Friedel–Crafts-type reaction to afford the unsymmetrical triarylmethane **4a**. This reaction mechanism hypothesis was supported by the fact that no reaction occurred with *N*-diarylmethyltosylamide and the reaction of **5** was much slower.

In summary, we have developed a facile synthesis of unsymmetrical arylbis(3-indolyl)methanes through the Brønsted acid catalyzed Friedel–Crafts alkylation of α-(3-indolyl)benzylamines with *N*-methylindole. This represents an interesting example that a useful method was developed by the inspiration of a side reaction. Ongoing efforts in our laboratory include the development of an asymmetric version of the current reaction, and the enantioselective synthesis of unsymmetrical triarylmethanes will be reported in due course.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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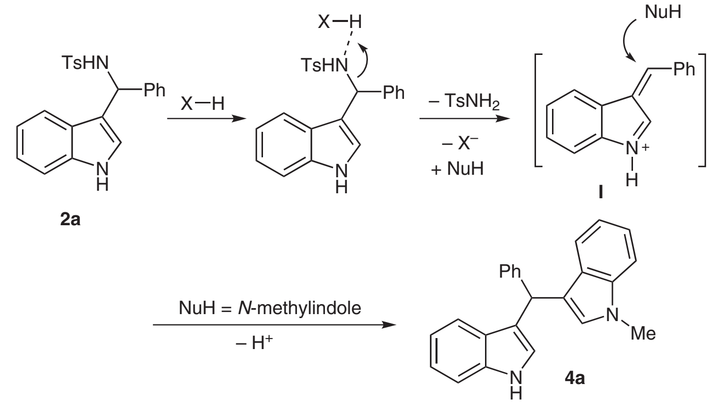
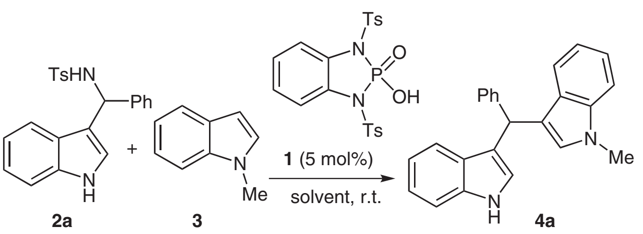


Scheme 3 The Brønsted acid catalyzed Friedel–Crafts alkylation of **2a** with *N*-methylindole

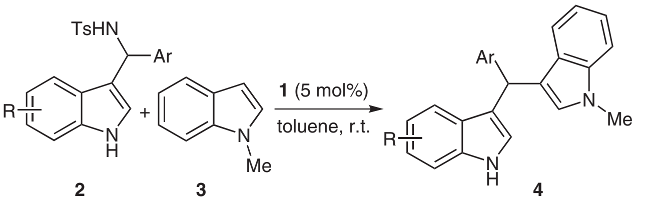
Table 1 Optimization of the Reaction Conditions for the Synthesis of Triarylmethanes



Entry[a]	Solvent	Time (h)	Yield (%)[b]
1	toluene	1.0	94
2	CH_2Cl_2	1.0	74
3	Et_2O	24.0	74
4	THF	24.0	30
5[c]	toluene	24.0	22
6[d]	toluene	1.0	67
7[e]	toluene	1.0	85

[a] Reaction conditions: **3** (0.3 mmol), **1** (5 mol%), **2** (0.2 mmol) in solvent (4 mL), r.t.
[b] Isolated yields.
[c] 5 mol% H_3PO_4 was used instead of **1**.
[d] 5 mol% TFA was used.
[e] 5 mol% TsOH·H_2O was used.

Table 2 Synthesis of Unsymmetrical Arylbis(3-indolyl)methanes[a]



Entry	**2** R	Ar	Time (h)	Yield of **4** (%)[b]
1	**2a** H	Ph	1	**4a** 94
2	**2b** H	4-$MeOC_6H_4$	0.1	**4b** 95
3	**2c** H	4-MeC_6H_4	0.1	**4c** 97
4	**2d** H	2-BrC_6H_4	22	**4d** 97
5[c]	**2e** H	4-BrC_6H_4	1	**4e** 95
6[c]	**2f** H	4-$O_2NC_6H_4$	16	**4f** 97
7[c]	**2g** H	3-$O_2NC_6H_4$	40	**4g** 83
8	**2h** 5-MeO	Ph	1	**4h** 93
9	**2i** 5-Me	Ph	1	**4i** 92
10	**2j** 5-Br	Ph	1	**4j** 74
11	**2k** 5-F	Ph	1	**4k** 72
12	**2l** 6-BnO	Ph	1	**4l** 74
13	**2m** 6-Br	Ph	5	**4m** 98
14	**2n** 4-Me	Ph	1	**4n** 66
15	**2o** 2-Me	Ph	2	**4o** 88

[a] Reaction conditions: **3** (0.3 mmol), **1** (5 mol%), **2** (0.2 mmol) in toluene (4 mL), r.t.
[b] Isolated yields.
[c] Reaction was carried out in CH_2Cl_2.

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(9) **General Procedure for the Synthesis of the Unsymmetrical Arylbis(3-indolyl)methanes in Table 2**
In a dry Schlenk tube, α-(3-indolyl)benzylamine **2** (0.20 mmol; see ref. 6 for the preparation) and phosphorodiamidic acid **1** (4.8 mg, 0.01 mmol) were dissolved in toluene (4 mL) under argon. *N*-Methylindole (39.3 mg, 0.30 mmol) was added and the solution was stirred at r.t. After the reaction was complete (monitored by TLC), sat. aq NaHCO$_3$ (3 mL) was added to quench the reaction. The mixture was extracted with EtOAc (10 mL). The organic layer was washed by brine (5 mL), separated, and dried over anhyd Na$_2$SO$_4$. The solvents were removed under reduced pressure, and the residue was purified by flash chromatography (EtOAc–PE, 1:8 to 1:5) to afford the product.

(10) **3-[(1-Methyl-1*H*-indol-3-yl)(phenyl)methyl]-1*H*-indole (Table 2, Entry 1)**
Prepared according to the general procedure to provide the title compound as a white solid (94% yield) following silica gel chromatography (EtOAc–PE, 1:6).
Analytical Data
^{1}H NMR (300 MHz, CDCl$_3$): δ = 3.65 (s, 3 H), 5.87 (s, 1 H), 6.49 (s, 1 H), 6.63 (s, 1 H), 6.69–7.02 (m, 2 H), 7.13–7.39 (m, 11 H), 7.82 (s, 1 H). ^{13}C NMR (75 MHz, CDCl$_3$): δ = 32.6, 40.1, 109.1, 111.0, 118.0, 118.6, 119.1, 119.7, 119.9, 120.0, 121.4, 121.8, 123.6, 126.0, 127.4, 126.0, 126.9, 127.4, 128.1, 128.2, 128.6, 136.5, 137.3, 144.1. IR (film): 3410, 3053, 2923, 1605, 1456, 1418, 1371, 1329, 1154, 1092, 1011, 740, 703, 580 cm^{-1}. HRMS (EI): *m/z* calcd for C$_{24}$H$_{20}$N$_2$: 336.1626; found: 336.1628.