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Enantioselective Synthesis of Unsymmetrical Triarylmethanes by Chiral Brønsted Acids

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Chiral Brønsted acid catalyzed Friedel–Crafts alkylation of electron-rich arenes with (3-indolyl)methanamines has been realized to provide an efficient synthesis of enantioenriched unsymmetrical triarylmethanes. With 5 mol-% of a newly developed chiral phosphoric acid, the enantioenriched unsymmetrical triarylmethanes were obtained in excellent yields with up to 91 % *ee*.

Introduction

The synthesis of triarylmethanes has attracted much attention from the synthetic community because of their versatile applications, such as biologically active compounds, protecting groups in organic synthesis, important dyes, etc.[1] Although significant progress has been made towards the synthesis of triarylmethanes,[2] the synthesis of unsymmetrical triarylmethanes remains challenging.[3] Moreover, the enantioselective synthesis of optically pure unsymmetrical triarylmethanes represents a major challenge to synthetic chemists. Very recently, Yu and co-workers reported an enantioselective synthesis of unsymmetrical triarylmethanes by a palladium-catalyzed desymmetrization of 2-pyridyl-derived triarylmethanes.[4] To the best of our knowledge, this is the only example for the catalytic enantioselective synthesis of unsymmetrical triarylmethanes.

During our recent study on the chiral phosphoric acid catalyzed Friedel–Crafts reaction of indole,[5–7] we have observed that a side reaction occurs to afford triarylmethane byproducts with two indole groups [Eq. (1), Figure 1].[7a] Given the great importance of indole-containing triarylmethanes[8] and the challenge for the synthesis of optically active unsymmetrical triarylmethanes, we recently found that the synthesis of unsymmetrical triarylmethanes could be obtained through a Brønsted acid (**1**) catalyzed Friedel–Crafts alkylation of (3-indolyl)methanamine with another electron-rich arene [Eq. (2), Figure 1].[9] In addition, we recently realized a chiral phosphoric acid catalyzed tandem double Friedel–Crafts reaction of indoles with 2-formylbiphenyl derivatives to afford fluorene derivatives with up to 96% *ee*.[7g] With these successes, we envisaged that the asymmetric synthesis of unsymmetrical triarylmethanes by

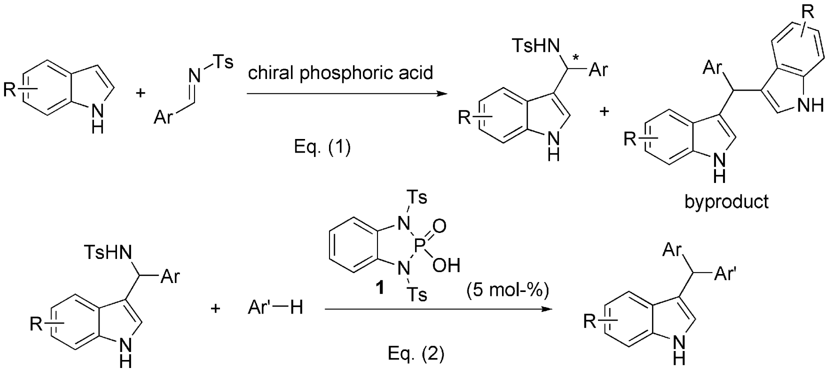

Figure 1. Synthesis of unsymmetrical triarylmethanes inspired by a side reaction.

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Friedel–Crafts alkylation of a (3-indolyl)methanamine with another electron-rich arene might be possible in the presence of a chiral phosphoric acid. In this paper, we report such a chiral phosphoric acid catalyzed enantioselective synthesis of unsymmetrical triarylmethanes.

Results and Discussion

With the previous success on the synthesis of unsymmetrical triarylmethanes,[9] we explored their asymmetric synthesis with chiral phosphoric acids (Figure 2). We began our studies with examining different chiral phosphoric acids for the Friedel–Crafts reaction of **2a** with **3**.

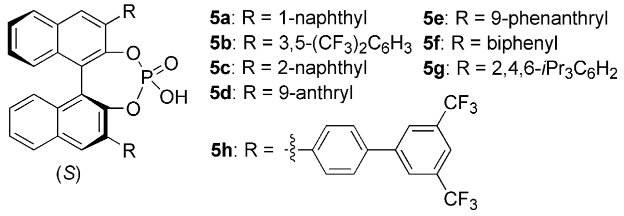


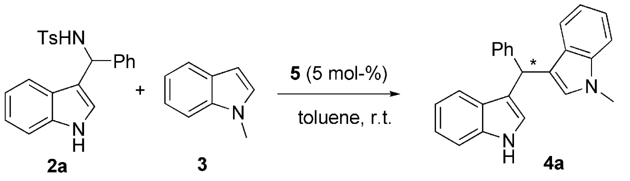
Figure 2. Several chiral Brønsted acids.

As summarized in Table 1, in the presence of 5 mol-% of **5a–g**, unsymmetrical triarylmethane **4a** was obtained with only moderate *ee* values. Interestingly, among all the tested catalysts known in the literature, acids **5b** bearing the 3,5-bis(trifluoromethyl)phenyl group and **5f** bearing the biphenyl group gave the highest *ee* values, 48% and 40%, respectively. With a straightforward design by synergistically combining these two groups, we synthesized the novel phosphoric acid **5h**. To our great delight, with 5 mol-% of **5h**, the reaction was much faster and led to triarylmethane **4a** in 91% yield with 58% *ee*. After further optimizing the reaction conditions, we found that benzene and *m*-xylene were suitable solvents, and a beneficial effect was also observed by adding molecular sieves (5 Å). Under these optimized reaction conditions, various (3-indolyl)methanamine derivatives were tested to examine the generality of the reaction. The results are summarized in Table 2.

With 2 mol-% of the catalyst, **4a** was obtained in 80% yield with 68% *ee* (Entry 1, Table 2). For the substitutents on the aryl group, electron-donating groups (4-MeO, 4-Me) were well tolerated to give their corresponding triarylmethanes in excellent yields with moderate *ee* values (Entries 2–3, Table 2). Substrate **2d** bearing an electron-withdrawing group (4-Br) underwent the reaction relatively slow to give triarylmethane **4d** in 64% yield with 61% *ee* (Entry 4, Table 2). Substrates with substitutents of different electronic properties on different positions of indole all led to the formation of corresponding unsymmetrical triarylmethanes, with up to 96% yield and 61% *ee* (Entries 5–10, Table 2).

Interestingly, when 1,3,5-trimethoxybenzene (**6**) was tested in the Friedel–Crafts-type reaction with **2**, chiral phosphoric acid **5a** was found to be the optimal catalyst (Scheme 1). With 5 mol-% of **5a**, unsymmetrical triarylmethanes **7a** and **7b** were obtained in 64% *ee* and 91% *ee*, respectively. However, the yields remained poor due to the formation of the dialkylation byproduct.

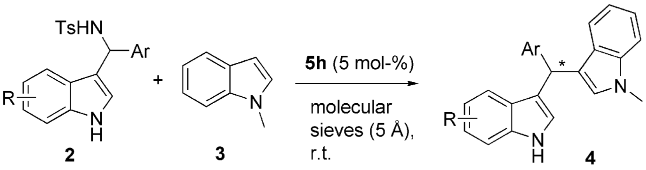
Table 1. Optimization of the reaction conditions for the asymmetric synthesis of unsymmetrical triarylmethanes.



Entry[a]	5	Time	Yield [%][b]	*ee* [%][c]
1	**5a**	2 d	84	24
2	**5b**	10 d	71	48
3	**5c**	19 h	88	33
4	**5d**	2 d	85	12
5	**5e**	6 d	73	15
6	**5f**	34 h	81	40
7[d]	**5g**	2 d	53	22
8	**5h**	5 h	91	58

[a] Reaction conditions: 0.15 mmol of **3**, 5 mol-% of **5**, 0.1 mmol of **2a** in 2 mL of toluene at room temp. [b] Isolated yields. [c] Determined by chiral HPLC analysis (Chiralcel OD-H column). [d] The reaction was carried out at 50 °C.

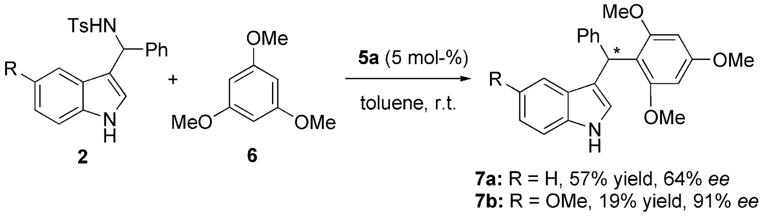
Table 2. Enantioselective synthesis of unsymmetrical triarylmethanes.



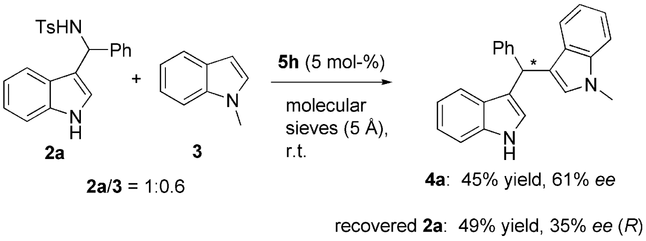
Entry[a]	**2**, Ar, R	Solvent	*t* [h]	**4**, yield [%][b]	*ee* [%][c]
1[d]	**2a**, Ph, H	benzene	10	**4a**, 80	68
2	**2b**, p-MeOC$_6$H$_4$, H	benzene	4	**4b**, 95	61
3	**2c**, p-MeC$_6$H$_4$, H	benzene	4	**4c**, 86	53
4	**2d**, p-BrC$_6$H$_4$, H	*m*-xylene	52	**4d**, 64	61
5	**2e**, Ph, 5-MeO	benzene	8	**4e**, 96	50
6	**2f**, Ph, 5-Me	benzene	11	**4f**, 95	59
7	**2g**, Ph, 5-Br	*m*-xylene	4	**4g**, 62	56
8	**2h**, Ph, 5-F	benzene	8	**4h**, 90	45
9	**2i**, Ph, 6-BnO	benzene	14	**4i**, 76	48
10	**2j**, Ph, 6-Br	*m*-xylene	46	**4j**, 61	61

[a] Reaction conditions: 1.2 equiv. of **2**, 5 mol-% of **5h**, 0.04 mol/L of **3** in benzene or *m*-xylene at room temp. [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] With 2 mol-% of the catalyst.

Another interesting feature of the current system is the kinetic resolution of the starting material (3-indolyl)methanamines. When the reaction was carried out with a ratio of 1:0.6 for **2a**/**3**, a mild kinetic resolution process was observed (Scheme 2); **2a** was recovered in 49% yield with 35% *ee* and (*R*) configuration. The same configuration of recovered **2a** as that obtained by the chiral phosphoric acid catalyzed Friedel–Crafts reaction of indole with an imine suggests that the formation of the dialkylation byproduct would increase the *ee* of the desired product.[7a]



Scheme 1. Friedel–Crafts reaction of **2** with 1,3,5-trimethoxybenzene (**6**).



Scheme 2. Kinetic resolution of **2a** with *N*-methylindole (**3**).

Conclusions

We have developed an enantioselective synthesis of unsymmetrical triarylmethanes by chiral phosphoric acid catalyzed Friedel–Crafts alkylation of (3-indolyl)methanamines with electron-rich arenes. In the presence of a newly developed chiral phosphoric acid, the unsymmetrical triarylmethanes were obtained with up to excellent yields and *ee* values.

Experimental Section

In a dry Schlenk tube, a mixture of (3-indolyl)methanamine derivative **2** (0.20 mmol), chiral phosphoric acid **5h** (7.4 mg, 0.008 mmol), freshly activated molecular sieves (5 Å) (50 mg) and benzene or *m*-xylene (4 mL) was stirred at room temperature under argon. *N*-Methylindole (**3**) (0.17 mmol) was added, and the solution was stirred at room temperature for several hours. After the reaction was complete (monitored by TLC), saturated aqueous $NaHCO_3$ (3 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate (10 mL). The organic layer was washed with brine (5 mL), separated, and dried with anhydrous Na_2SO_4. The solvents were removed under reduced pressure, and the residue was purified by flash chromatography (ethyl acetate/petroleum ether, 1:8 to 1:5) to afford the product.

Supporting Information (see footnote on the first page of this article): Experimental details, copies of ^{1}H and ^{13}C NMR spectra, HPLC diagrams of **4**.

Acknowledgments

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