We disclose herein a highly enantioselective protocol for the Brønsted acid-catalyzed addition of indoles and phenols to \textit{in situ}-generated \textit{ortho}-quinone methides which deliver broadly substituted diarylindolylmethanes and triarylmethanes, respectively, in a one-pot reaction under very mild conditions. A chiral phosphoric acid catalyst has been developed for this process serving to convert the starting \textit{ortho}-hydroxybenzhydryl alcohols into the reactive \textit{ortho}-quinone methides and to control the enantioselectivity of the carbon–carbon bond-forming event via hydrogen-bonding.

Triarylmethanes have gained substantial attention from the synthetic community because of their importance in medicinal chemistry, materials science and as dye precursors. Several of them are known to be potential drug candidates for the treatment of cancer, bacterial infections, and diabetes and are also core structures in natural products such as for example in cassigapor B. Similarly, heteroaryl-substituted analogues of this product class have been shown to be powerful pharmaceuticals and bioactive molecules like letrozole, vorozole, and paraphenyl-substituted diindolylmethanes. Accordingly, novel synthetic methods to access enantioselectively highly enriched triarylmethanes and related compounds continue to be highly desirable.

Although a variety of racemic routes have been developed only a few enantioselective syntheses are currently available based upon reports from the groups of Jarvo, Watson, and Crudden who employed asymmetric cross-coupling technology to construct the target triarylmethanes in the optically highly enriched form. Apart from that You, Zhang, and Han developed Brønsted acid-catalyzed, enantioselective syntheses of special aryldiindolylmethanes starting from both aryl(3-indolyl)-methanols and aryl(2-indolyl)methanols.

Recently, we have disclosed the phosphoric acid-catalyzed, highly enantioselective conjugate addition of 1,3-dicarbonyl compounds to \textit{in situ} generated \textit{ortho}-quinone methides (\textit{o-QM}). This strategy was applied to a one-pot and straightforward synthesis of optically highly enriched 4-aryl-4\textit{H}chromenes and related heterocycles through a subsequent cyclodehydration reaction (Scheme 1, pathway a). \textit{o-QM} constitute highly reactive synthetic intermediates participating easily in conjugate additions, hetero Diels–Alder reactions, and \(6\pi\)-electrocyclizations. It was only recently that a range of catalytic, enantioselective processes have been successfully developed for \textit{o-QM} chemistry including palladium-, cinchona alkaloid-, BINOL- and NHC-catalyzed reactions.

In continuation of our interest in enantioselective reactions of hydrogen-bonded \textit{o-QM} we now report that both indoles and naphthols are highly suitable nucleophiles for this purpose and deliver broadly substituted diarylindolylmethanes and triarylmethanes with excellent yields and enantioselectivities (Scheme 1, pathway b). Bach and coworkers pursued this strategy previously and obtained some addition products with moderate enantioselectivity. Very recently Sun \textit{et al.} have shown that tertiary benzylic alcohols can form triarylmethanes that carry exclusively quaternary chiral centers upon indole addition.
We initiated our studies by investigating the reaction of ortho-hydroxybenzhydryl alcohol 1a (1 equiv.) with indole (2a) (1.2 equiv.) in CH$_2$Cl$_2$ in the presence of various chiral phosphoric acids 3a-g (5 mol%) (Table 1). The (F–C) adduct 4a was obtained in good yields in almost all cases within 2.5 h at room temperature. Systematic screening of the catalysts further revealed that sterically demanding 3,3'-aryl substituents in the BINOL-backbone of the Brønsted acid catalyst gave improved enantioselectivities. An optimal selectivity was eventually obtained with phosphoric acid 3d (Ar = 2,6-Me$_2$-4'-BuC$_6$H$_2$) which delivered the (F–C) addition product 4a with 94% yield and 91.9:9 er (Table 1, entry 4). Solvents like toluene and CH$_3$CN were found to be inferior as compared to CH$_2$Cl$_2$, reducing the selectivity to 79:21 er and 81:19 er, respectively, albeit in excellent yields (entries 9 and 10). The amount of indole was further reduced to 0.27 mmol (1.2 equiv.) in CH$_2$Cl$_2$ in the presence of various chiral phosphoric acid (Ar = 2,6-Me$_2$-4'-BuC$_6$H$_2$) and 5 mol% of catalyst 3d in 3 mL of CH$_2$Cl$_2$ at rt. Isolated yield of the purified product. Reaction was carried out at 0 °C. 1.0 equiv. of indole (2a) was used as the substrate.

Table 1 Optimization studies

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Er (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>CH$_2$Cl$_2$</td>
<td>1.5</td>
<td>96</td>
<td>80:20</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>CH$_2$Cl$_2$</td>
<td>1.5</td>
<td>97</td>
<td>89:11</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>CH$_2$Cl$_2$</td>
<td>2</td>
<td>94</td>
<td>80:20</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>CH$_2$Cl$_2$</td>
<td>1.5</td>
<td>94</td>
<td>91:9</td>
</tr>
<tr>
<td>5</td>
<td>3e</td>
<td>CH$_2$Cl$_2$</td>
<td>1.5</td>
<td>94</td>
<td>72:28</td>
</tr>
<tr>
<td>6</td>
<td>3f</td>
<td>CH$_2$Cl$_2$</td>
<td>1.5</td>
<td>96</td>
<td>89:11</td>
</tr>
<tr>
<td>7</td>
<td>3h</td>
<td>CH$_2$Cl$_2$</td>
<td>1.5</td>
<td>97</td>
<td>65:35</td>
</tr>
<tr>
<td>8d</td>
<td>3d</td>
<td>CH$_2$Cl$_2$</td>
<td>1.5</td>
<td>97</td>
<td>86:14</td>
</tr>
<tr>
<td>9</td>
<td>3d</td>
<td>CH$_2$CN</td>
<td>2.5</td>
<td>96</td>
<td>79:21</td>
</tr>
<tr>
<td>10</td>
<td>3d</td>
<td>Toluene</td>
<td>1.5</td>
<td>94</td>
<td>81:19</td>
</tr>
<tr>
<td>11f</td>
<td>3d</td>
<td>CH$_2$Cl$_2$</td>
<td>1.5</td>
<td>92</td>
<td>92:8</td>
</tr>
</tbody>
</table>

All reactions were carried out with 0.23 mmol (1 equiv.) of 1a, 0.27 mmol (1.2 equiv.) of 2a and 5 mol% of catalyst 3a-3f in 3 mL of CH$_2$Cl$_2$ at rt. Isolated yield of the purified product. Reaction was carried out at 0 °C. 1.0 equiv. of indole (2a) was used as the substrate.

In addition, the influence of various functional groups and substituents in the indole component was investigated in this study (Table 3). These results clearly reveal an excellent functional group tolerance of this process and a broad set of heteroaryl-substituted triarylmethanes was obtained in good yields and enantioselectivities irrespective of the electronic properties of the substituents on the indole ring.

Challenging substituents like phenol, formyl, acid, cyano, ester, ether, and halide groups did not interfere with this process and both within the o-QM fragment as well as the β-aryl substituent delivering the products with excellent results as well.

A crystal structure of diarylindolylmethane 4c (entry 2) obtained by slow evaporation of CH$_2$Cl$_2$ revealed its absolute configuration which was assigned to all other products as well (Fig. 1).18
furnished the desired (F–C) addition products in good to excellent enantioselectivities and high yields. The ability to withstand all these functional groups without compromising the yield or selectivity is testimony to the scope of this methodology.

The excellent results obtained for indoles inspired us to pursue this strategy further and extend it to electron-rich naphthols which are also known to be excellent substrates to undergo (F–C) alkylation reactions. A range of Brønsted acid catalysts were screened for the (F–C) alkylation of naphthol (1a) with ortho-hydroxybenzhydrol 1a (see the ESI). It turned out that in the presence of 5 mol% of catalysts 3a–c and 3d, respectively, the unsymmetrically substituted triarylmethanes were obtained in excellent yields in all cases studied. The highest enantioselectivity was obtained again with catalyst 3d when 4 Å MS was used as an additive in CH₂Cl₂ as the solvent at room temperature.

With these conditions established we examined a range of 2-naphthols in reactions of hydrogen-bonded o-QM (Table 4). A series of differently substituted ortho-hydroxybenzhydrol alcohols were tested as o-QM precursors (entries 1–7). In almost all cases studied the triarylmethanes 17a–g were isolated in excellent yields and with >96 : 4 er. Further substitution within the 2-naphthol ring with halogen, ester, ether, and aryl substituents was readily tolerated and delivered the products 17h–m in comparably high yields and enantioselectivities (entries 8–13). Quite interestingly, 1-naphthol (16) worked equally well as the substrate and furnished triarylmethane 18 in almost quantitative yield and 93:7 er (entry 14).

To further reveal the synthetic potential of this new process some of the diarylindolymethanes were subsequently converted into highly versatile dihydrochromeno[2,3-b]indoles 19a–b through a one-pot bromination followed by cyclization and base-catalyzed elimination (Scheme 2). The products were obtained in good yields and retained their optical purity almost completely.

On the basis of the crystal structure which we obtained for the (F–C)-product 4c, we propose a transition structure as shown in Fig. 2, which accommodates double hydrogen-bonding of the catalyst to both the o-QM and the nucleophile and intramolecular delivery of the nucleophile to the re-face of the o-QM because the opposite face is effectively shielded by the neighbouring 3′-Ar-group.

In summary, we have developed a highly efficient, Brønsted acid-catalyzed (F–C)-alkylation of electron-rich indoles and the 2-naphthol ring with halogen, ester, ether, and aryl substituents was readily tolerated and delivered the products 17h–m in comparably high yields and enantioselectivities (entries 8–13). Quite interestingly, 1-naphthol (16) worked equally well as the substrate and furnished triarylmethane 18 in almost quantitative yield and 93:7 er (entry 14).

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naphthols with in situ-generated 6-QM which furnished a broad range of synthetically useful diarylindolylmethanes and triaryl-
methanes with excellent yields and enantioselectivities. The diarylindolylmethanes were subsequently converted into valu-
able dihydropyridinom(2,3-b)indoles through a base-catalyzed addition–elimination reaction with full retention of absolute configura-
tion. This study further underlines the utility and power of phosphoric acid-catalyzed, enantioselective reactions of 6-QM and signifi-
cantly extends the scope of this strategy.

We thank Dr P. Lönecke (University of Leipzig) for the crystal structure analysis. We gratefully acknowledge the donation of chemicals from Evonik and BASF.

Notes and references


