Highly Stereoselective Synthesis of trans-1,2-Cyclopropane Derivatives from Semistabilized Arsonium Ylides by Phase-Transfer-Catalysis Reactions

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A variety of arsonium ylides have been investigated in organic synthesis.† These ylides have also been used in the stereoselective synthesis of cyclopropane derivatives, which can easily be converted into other diverse and useful building blocks.‡ They can be prepared by treating the corresponding arsenides with high stereoselectivity. However, less attention has been paid to the production of many types of new compounds with high stereoselectivity.5

We further studied the reaction of 4-nitrobenzyltriphenylarsorane (1b) with 5-substituted-benzylidenecyclopropanes containing a strong electron-withdrawing substituent such as 3a was used as substrate, no product 4ae was observed in this reaction with arsonium ylide 2a (Table 1, entries 1–5).

We described the phase-transfer-catalyzed cyclopropanation reaction of semistabilized arsonium ylides to afford trans-1,2-cyclopropane derivatives with high stereoselectivity. The synthesis of trans-1,2-cyclopropane derivatives in the presence of sodium hexamethyldisilazanide (1.0 M solution in THF) were also studied. Benzylidenetriphenylarsorane (2a), generated in situ from the corresponding benzyltriphenylarsorane bromide (1a) in the biphasic system of dichloromethane–50% aqueous sodium hydroxide solution, reacted with 5-benzylidene-2,2-dimethyl-1,3-dioxane-4,6-diones 3a–e at room temperature for one hour to afford trans-1-aryl-6,6-dimethyl-5,7-dioxo-2-phenylspiro[2.5]octane-4,8-diones 4aa–ad in 61–86% yields by a phase-transfer-catalyzed reaction with high stereoselectivity. It is worth noting that the triphenylarsine 6 could be recovered. If compound 3 containing a strong electron-withdrawing substituent such as 3e was used as substrate, no product 4ae was observed in this reaction with arsonium ylide 2a (Table 1, entries 1–5).

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forded trans/cis-1,2-cyclopropane derivatives 4bb/5bb and 4be/5be in high yields and the stereoselectivity decreased greatly, probably because arsonium ylide 2b was more easily generated in situ from the corresponding arsonium bromide 1b in the biphasic system of dichloromethane–50% aqueous sodium hydroxide solution than arsonium ylide 2a. In this case, the cyclopropanation reaction from 4-nitrobenzylidetriphenylarsorane (2b) was fast, but with low stereoselectivity.

We found trans-1-aryl-6,6-dimethyl-2-(4-methylphenyl)-5,7-dioxospiro[2.5]octane-4,8-diones 4ca–cd were also obtained from 4-methylbenzylidenetriphenylarsorane (2c) with 5-substituted-benzylidene 2,2-dimethyl-1,3-dioxane-4,6-diones 3a–e at room temperature for 40 minutes by phase-transfer-catalyzed reaction with high stereoselectivity. If compounds 3 containing an electron-donating substituent on aryl such as 3a,b were used as the substrate, trans-1,2-cyclopropane derivatives 4ca and 4cb were formed at room temperature in good yields. If compound 3 containing a strong electron-withdrawing substituent such as 3e was used as the substrate, no product 4ce was observed in the reaction with arsonium ylide 2c (Table 1, entries 11–15). The cyclopropanation reaction from 4-methylbenzylidenetriphenylarsorane (2c) was slow, but with higher stereoselectivity as compared to 4-nitrobenzylidenetriphenylarsorane (2b).

In the cyclopropanation reaction of semistabilized arsonium ylide 2a,c with electron-deficient alkenes 3a–e by phase-transfer-catalyzed reaction, we observed that there is a relationship between the reactivity and the electronic nature of substituent Y. As the substituent Y becomes more strongly electron-donating, the yield of 4 increases and the reactivity improves; when Y becomes more strongly electron-withdrawing, the yield decreases and the reactivity is weakened.

### Table 1 Preparation of Cyclopropane Derivatives 4aa–cd and 5bb,be by a Phase-Transfer-Catalysis Reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>As salt</th>
<th>X</th>
<th>Alkene</th>
<th>Y</th>
<th>Product</th>
<th>Ratio(^{a}) (trans/cis)</th>
<th>Temp (°C)</th>
<th>Yield(^{b}) (%)</th>
<th>mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>H</td>
<td>3a</td>
<td>OMe</td>
<td>4aa</td>
<td>trans</td>
<td>r.t.</td>
<td>86</td>
<td>94–95</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>H</td>
<td>3b</td>
<td>Me</td>
<td>4ab</td>
<td>trans</td>
<td>r.t.</td>
<td>77</td>
<td>148–149</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>H</td>
<td>3c</td>
<td>H</td>
<td>4ac</td>
<td>trans</td>
<td>r.t.</td>
<td>75</td>
<td>167–169</td>
</tr>
<tr>
<td>4</td>
<td>1a</td>
<td>H</td>
<td>3d</td>
<td>Cl</td>
<td>4ad</td>
<td>trans</td>
<td>r.t.</td>
<td>61</td>
<td>162–163</td>
</tr>
<tr>
<td>5</td>
<td>1a</td>
<td>H</td>
<td>3e</td>
<td>NO(_2)</td>
<td>4ae</td>
<td>–</td>
<td>r.t.</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>1b</td>
<td>NO(_2)</td>
<td>3a</td>
<td>OMe</td>
<td>4ba</td>
<td>–</td>
<td>r.t.</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>1b</td>
<td>NO(_2)</td>
<td>3b</td>
<td>Me</td>
<td>4bb/5bb</td>
<td>4:1</td>
<td>r.t.</td>
<td>94</td>
<td>141–142/119–120</td>
</tr>
<tr>
<td>8</td>
<td>1b</td>
<td>NO(_2)</td>
<td>3c</td>
<td>H</td>
<td>4bc</td>
<td>trans</td>
<td>r.t.</td>
<td>96</td>
<td>158–159</td>
</tr>
<tr>
<td>9</td>
<td>1b</td>
<td>NO(_2)</td>
<td>3d</td>
<td>Cl</td>
<td>4bd</td>
<td>trans</td>
<td>r.t.</td>
<td>98</td>
<td>173–174</td>
</tr>
<tr>
<td>10</td>
<td>1b</td>
<td>NO(_2)</td>
<td>3e</td>
<td>NO(_2)</td>
<td>4be/5be</td>
<td>3:1</td>
<td>r.t.</td>
<td>93</td>
<td>176–177/229–230</td>
</tr>
<tr>
<td>11</td>
<td>1c</td>
<td>Me</td>
<td>3a</td>
<td>OMe</td>
<td>4ca</td>
<td>trans</td>
<td>r.t.</td>
<td>80</td>
<td>108–109</td>
</tr>
<tr>
<td>12</td>
<td>1c</td>
<td>Me</td>
<td>3b</td>
<td>Me</td>
<td>4cb</td>
<td>trans</td>
<td>r.t.</td>
<td>78</td>
<td>164–165</td>
</tr>
<tr>
<td>13</td>
<td>1c</td>
<td>Me</td>
<td>3c</td>
<td>H</td>
<td>4cc</td>
<td>trans</td>
<td>r.t.</td>
<td>45</td>
<td>148–149</td>
</tr>
<tr>
<td>14</td>
<td>1c</td>
<td>Me</td>
<td>3d</td>
<td>Cl</td>
<td>4cd</td>
<td>trans</td>
<td>r.t.</td>
<td>7</td>
<td>166–167</td>
</tr>
<tr>
<td>15</td>
<td>1c</td>
<td>Me</td>
<td>3e</td>
<td>NO(_2)</td>
<td>4ce</td>
<td>–</td>
<td>r.t.</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

\(^{a}\) Determined by \(^{1}\)H NMR.

\(^{b}\) Isolated yields.
A similar cyclopropanation was studied. Benzylidene-triphenylarsorane (2a), generated in situ from the corresponding benzyltriphenylarsonium bromide (1a) in the presence of sodium hexamethyldisilazanide (1.0 M solution in THF), reacted at room temperature with electron-deficient alkenes 3a–d to afford trans-1,2-cyclopropane derivatives 4aa–ad in 33–53% yields with high stereoselectivity (Table 2, entries 1–4). However, the yields were less improved by lowering the reaction temperature from room temperature to –78 °C (Table 2, entries 6–9). If compound 3 containing a strong electron-withdrawing substituent such as 3e was used as the substrate, trans-1,2-cyclopropane derivatives 4ae and cis-1,2-cyclopropane derivatives 5ae could be observed at room temperature or –78 °C (Table 2, entries 5 and 10). The ratios of trans/cis isomers (4ae/5ae) were 4:1 and 2:1, respectively. As compared with two synthesis methods, we found that the cyclopropanation reaction the phase-transfer-catalyzed reaction is simpler and gives higher yields.

It is worth mentioning that this cyclopropanation reaction is highly stereoselective. The structures of the products 4aa–cd were established by 1H and 13C NMR, IR, and HRMS. The relative stereochemistry of the products 4 was established by the 1H NMR and 2D NOESY. The trans configuration of 1,2-cyclopropane derivatives 4ab and 4bb was confirmed by 2D NOESY, showing no NOE effect for the two vicinal cyclopropyl protons (Figure 1 and Figure 2). The structure of trans-1,2-cyclopropane derivative 4ab was also confirmed by X-ray diffraction analysis (Figure 3). In all of the products 4aa–cd, the
The coupling constants of the two vicinal cyclopropyl protons were around 10.0 Hz. Based on these results, we deduce that the vicinal cyclopropyl protons of 4ab–cd are trans. The cis configuration of 1,2-cyclopropane derivative 5bb was also confirmed by 2D NOESY, showing an NOE effect for the two vicinal cyclopropyl protons (Figure 4). In all of the products 5ad,bb,be, the coupling constants of the two vicinal cyclopropyl protons were about 10.5 Hz. Based on these results, we deduce that the vicinal cyclopropyl protons of 5ad,bb,be are cis. The trans,trans-configuration of γ-butyrolactone derivative 7 was assumed by 2D NOESY (Figure 5), which shows there is no NOE effect for the vicinal protons.

In summary, we have demonstrated the phase-transfer-catalyzed reaction of semistabilized arsonium ylide 2a–c, which is generated in situ from the corresponding arsonium salts 1a–c, with electron-deficient alkenes 3a–e is an efficient and simple approach for the synthesis of trans-1-aryl-6,6-dimethyl-5,7-dioxo-2-(4-substituted phenyl)spiro[2.5]octane-4,8-diones 4aa–cd in good yields with high stereoselectivity. The simplicity of the procedure and the high stereoselectivity should offer great promising for the synthesis of trans-1,2-cyclopropane derivatives.
trans-2-(4-Chlorophenyl)-6,6-dimethyl-5,7-dioxo-1-phenylspiro[2.5]octane-4,8-dione (4ad)
White solid; yield: 217 mg (61%); mp 162–163 °C.
IR (KBr): 1765, 1732, 1317 cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 1.74 (s, 3 H), 1.75 (s, 3 H), 4.16 (d, J = 10.0 Hz, 1 H), 4.37 (d, J = 10.0 Hz, 1 H), 7.33–8.25 (m, 9 H).
13C NMR (125 MHz, CDCl₃): δ = 28.1, 28.4, 42.0, 46.3, 105.4, 123.8, 128.9, 129.2, 130.5, 131.2, 140.5, 147.9, 163.6, 164.8.

1-Aryl-6,6-dimethyl-2-(4-nitrophenyl)-5,7-dioxospiro[2.5]octane-4,8-diones 4bb–be; General Procedure by PTC
The reaction of 4-nitrobenzyltriphenylarsonium bromide (1b, 1.2 mmol) with 3a–e (1 mmol) and 50% aq NaOH (4 drops) was similar to that of benzyltriphenylarsonium bromide (1a). Compounds 4bb–be and 5bb, 5be were synthesized at r.t. for ~10 min. The ratios of trans/cis isomers (4bb/5bb and 4be/5be) were 4:1 and 4:3, respectively (1H NMR analysis).

trans-6,6-Dimethyl-1-(4-phenylphenyl)-2-(4-nitrophenyl)-5,7-dioxospiro[2.5]octane-4,8-dione (4bc)
White solid; yield: 148 mg (86%); mp 165–166 °C.
IR (KBr): 1765, 1732, 1316 cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 1.74 (s, 3 H), 1.75 (s, 3 H), 4.06 (d, J = 10.0 Hz, 1 H), 4.40 (d, J = 10.0 Hz, 1 H), 7.20–8.24 (m, 9 H).
13C NMR (125 MHz, CDCl₃): δ = 28.0, 28.1, 39.0, 44.8, 45.7, 55.4, 104.6, 114.0, 124.1, 128.4, 128.5, 129.4, 130.7, 132.7, 159.8, 164.5, 164.7.
Anal. Calcd for C₂₀H₁₇NO₆: C, 71.84; H, 5.72. Found: C, 70.70; H, 5.59.

trans-2-(4-Methoxyphenyl)-6,6-dimethyl-5,7-dioxo-1-phenylspiro[2.5]octane-4,8-dione (4aa)
White solid; yield: 302 mg (86%); mp 94–95 °C.
IR (KBr): 1763, 1731, 1520, 1310 cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 1.72 (s, 3 H), 1.73 (s, 3 H), 3.82 (s, 3 H), 4.25 (d, J = 10.0 Hz, 1 H), 4.33 (d, J = 10.0 Hz, 1 H), 6.89–7.38 (m, 9 H).
13C NMR (125 MHz, CDCl₃): δ = 28.1, 28.2, 38.8, 43.8, 45.5, 105.0, 128.7, 128.8, 129.5, 130.8, 131.1, 132.0, 134.5, 164.2, 164.6.
cis-6,6-Dimethyl-1-(4-methylphenyl)-2-(4-nitrophenyl)-5,7-dioxospiro[2.5]octane-4,8-dione (5ae)

White solid; yield: 151 mg (45%); mp 148–149 °C. The data of 5ae is identical to the data of 4ab.

trans-1-(4-Chlorophenyl)-6,6-dimethyl-1-(4-(4-methylphenyl)-5,7-dioxospiro[2.5]octane-4,8-dione (4cd)

White solid; yield: 26 mg (7%); mp 166–167 °C.

1H NMR (500 MHz, CDCl3): δ = 1.719 (s, 3 H), 1.723 (s, 3 H), 2.36 (s, 3 H), 4.18 (d, J = 10.0 Hz, 1 H), 4.29 (d, J = 10.0 Hz, 1 H), 7.17–7.35 (m, 8 H).

13C NMR (125 MHz, CDCl3): δ = 29.7, 28.0, 36.3, 45.3, 50.6, 52.0, 104.8, 114.6, 131.2, 131.2, 138.3, 147.5, 161.6, 167.9.

MS: m/z (%): 145 (29), 172 (90), 292 (26), 335 (1).

trans-6,6-Dimethyl-1-(4-(4-methoxyphenyl)-5,7-dioxo-2-phenylspiro[2.5]octane-4,8-dione (4be)

White solid; yield: 72 mg (19%); mp 119–120 °C.

1H NMR (500 MHz, CDCl3): δ = 1.73 (s, 3 H), 2.36 (s, 6 H), 4.29 (s, 2 H), 7.34–7.35 (m, 8 H).

13C NMR (125 MHz, CDCl3): δ = 65.72; H, 4.77; N, 3.66.


trans-1-Aryl-6,6-dimethyl-5,7-dioxo-2-phenylspiro[2.5]octane-4,8-dione (4ae)

White solid; mp 158–159 °C. The data of 4ae and 4bc are identical.

cis-6,6-Dimethyl-2-(4-(4-methylphenyl)-5,7-dioxospiro[2.5]octane-4,8-dione (5ac)

White solid; mp 155–156 °C.

IR (KBr): 3435.0810.

1H NMR (500 MHz, CDCl3): δ = 7.37 (m, 8 H), 7.34–7.35 (m, 8 H).

13C NMR (125 MHz, CDCl3): δ = 105.2, 123.2, 128.5, 128.8, 129.8, 131.2, 132.1, 138.9, 148.2, 163.8.


trans-1-(4-Methoxyphenyl)-6,6-dimethyl-2-(4-(4-methylphenyl)-5,7-dioxospiro[2.5]octane-4,8-dione (4ca)

White solid; yield: 293 mg (80%); mp 108–109 °C.

IR (KBr): 3478.4980.

1H NMR (500 MHz, CDCl3): δ = 1.71 (s, 3 H), 1.72 (s, 3 H), 2.35 (s, 3 H), 3.81 (s, 3 H), 4.25 (d, J = 10.0 Hz, 1 H), 4.28 (d, J = 10.0 Hz, 1 H), 6.89–7.32 (m, 8 H).

13C NMR (125 MHz, CDCl3): δ = 29.7, 28.10, 28.12, 39.2, 45.2, 45.6, 55.5, 104.8, 114.1, 124.4, 129.4, 129.6, 130.7, 138.4, 159.8, 164.7.

MS: m/z (%) = 118 (100), 282 (15), 308 (2).

trans-6,6-Dimethyl-1,2-bis(4-methylphenyl)-5,7-dioxospiro[2.5]octane-4,8-dione (4be)

White solid; yield: 268 mg (75%); mp 144–145 °C.

IR (KBr): 3111, 1781, 1751, 1608, 1520, 1350, 1171, 1007, 838 cm–1.
$^1$H NMR (500 MHz, acetone-d$_6$): $\delta = 3.84$ (s, 3 H), 4.31 (dd, $J = 10.5, 12.5$ Hz, 1 H), 4.52 (d, $J = 12.5$ Hz, 1 H), 5.72 (d, $J = 10.5$ Hz, 1 H), 6.98–8.28 (m, 8 H), 11.81 (br, 1 H).

$^{13}$C NMR (125 MHz, acetone-d$_6$): $\delta = 55.2, 55.5, 55.7, 85.4, 115.1, 124.8, 128.7, 129.4, 130.5, 144.4, 148.8, 161.5, 168.5, 170.6$.

HRMS: $m/z [M + Na]^+ \text{calcd for } C_{18}H_{15}NO_7: 380.07408$; found: 380.0757.

Acknowledgment
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References
(7) The crystal structure of 4ab has been deposited at the Cambridge Crystallographic Data Centre with the deposition number CCDC 671899. Unit cell parameters: $a = 9.5560$ (14) Å, $b = 10.0612$ (15) Å, $c = 10.3985$ (16) Å, $\alpha = 89.764$ (2), $\beta = 67.498$ (2), $\gamma = 74.565$ (2), space group: $P\bar{1}$.