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A chemoselective route to either 4-methyl-2,4-diphenyl-2-pentene or 1,1,3-trimethyl-3-phenylindane from 2-phenylpropan-2-ol mediated by $BiBr_3$: a mechanistic study

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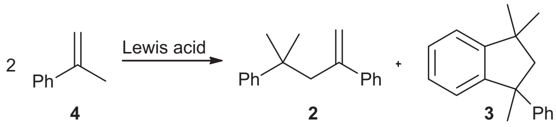
ABSTRACT

The reaction of 2-phenylpropan-2-ol mediated by $BiBr_3$ can, through control of the temperature, yield selectively either 4-methyl-2,4-diphenyl-2-pentene or 1,1,3-trimethyl-3-phenylindane. A reaction mechanism that proceeds via 1-methylstyrene is disclosed.

The development of new, efficient and preferably catalytic protocols for carbon–carbon bond-forming reactions is important in organic synthesis.[1] With few exceptions, these reactions include stoichiometric generation of waste formed from the leaving group.[2] Lewis acid-catalyzed dimerization of 1-methylstyrene (**4**) to yield a mixture of 4-methyl-2,4-diphenyl-1-pentene (**2**) and 1,1,3-trimethyl-3-phenylindane (**3**) is an example of a carbon–carbon bond-forming transformation that proceeds without generating a stoichiometric amount of waste (Scheme 1).[3] During the reaction to form **2**, a new carbon–carbon bond is formed, and in the cyclization to **3** a second new carbon–carbon bond is installed. The reaction proceeds with Markovnikov selectivity in both carbon–carbon bond-forming steps. Several Lewis acids,[4] including $FeCl_3$, $AlCl_3$,[4a] $BiCl_3$[4b] and $RuCl_3$,[4c] and also Brönsted acids have been reported to catalyze this reaction.[3,5] Unsaturated dimer **2** is an important chain transfer reagent in the production of polymers.[6] Therefore, chemoselective and high yielding reactions that generate **2** are highly desirable. However, all the previously reported catalytic reactions, except those catalyzed by Ru, are selective towards **3**.[4c]

Whereas there are several reports on the dimerization of **4**, there are only a limited number describing the formation of a mixture of **2** and **3** from 2-phenylpropan-2-ol (**1**) by Lewis[7] or Brönsted[8] acid catalysis. In most of these reports, a mixture of **2** and **3** is formed, and in most cases compound **3** predominates. Furthermore, the mechanism for the generation of **2** and **3** was not elucidated.

Due to the importance of being able to generate **2** selectively, we decided to study the reaction mechanism starting from 2-phenylpropan-2-ol (**1**). In the course of this study, important intermediates were observed giving insight into the reaction mechanism.

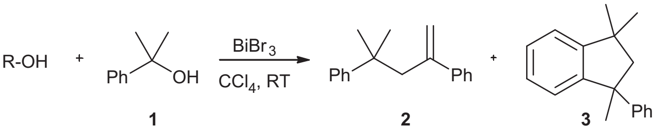


Scheme 1. Dimerization of 1-methylstyrene **4**.

Also, the equilibration of the intermediates was studied. Furthermore, a chemoselective reaction pathway to generate either **2** or **3** was developed.

In an attempt to reproduce cross etherification of **1** and 1-butanol or methanol with a stoichiometric amount of $BiBr_3$ in CCl_4, products **2** and **3** were formed in an 87.5:12.5 ratio without the involvement of the aliphatic alcohol (Scheme 2).[9] Compound **2** showed characteristic signals in the ^1H NMR spectrum at δ 1.34, 2.95, 4.90 and 5.26, and compound **3** exhibited resonances at δ 1.13, 1.44, 1.79, 2.29 and 2.52. The structural assignments were also in agreement with the ^{13}C NMR spectra in which characteristic signals were observed at δ 29.9, 39.8, 50.5 and 117.8 for **2** and at δ 30.4, 30.6, 30.8, 44.1, 52.1 and 60.6 for **3**.[4a]

With the aim to develop a reaction selective towards **2** different reaction parameters were screened. Increasing the ratio of the aliphatic alcohol did not affect the outcome of reaction nor did the addition of water. The reaction was robust and gave the same results in wet solvents and in air and when using purified reagents



Scheme 2. Unexpected dimerization of **1**.

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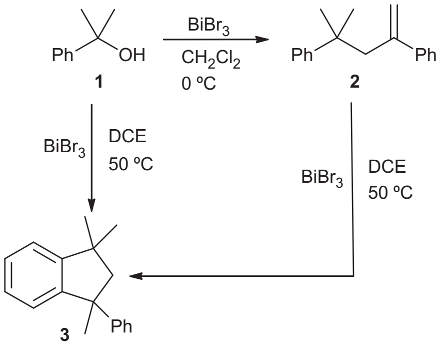
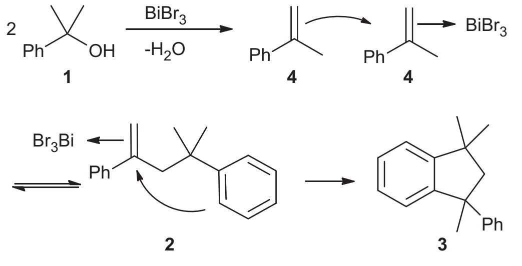


Scheme 3. Temperature dependence of the formation of **2** and **3**.

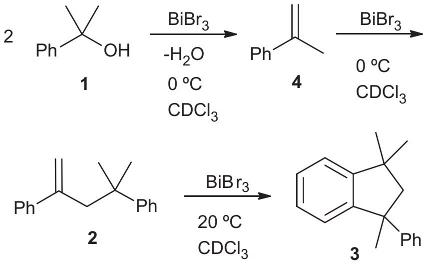
and an inert atmosphere. However, the reaction outcome was dependent on the temperature. When the reaction was run at 0 °C, product **2** was formed in 88% isolated yield after column chromatography (Scheme 3).[10] When the reaction was run at 50 °C, indane **3** was generated in above 95% conversion and in 82% yield. The fact that **2** was generated at lower temperatures implies that it is the kinetic product and **3** is the thermodynamic product. This was supported by transforming **2** into **3** in the presence of $BiBr_3$ at 50 °C in a separate experiment.[11] The dimerization of **1** could be performed using catalytic amounts of $BiBr_3$, albeit with a lower reaction rate. When the reaction was run using 5 mol % of $BiBr_3$, 60% of **1** was converted into the product within 2 h.[12]

When alcohol **1** was used as the starting material a possible reaction mechanism includes elimination of water to generate **4** (Scheme 4). This was proposed by Stavber's group.[7a] The Lewis acid coordinates to the double bond in **4**, which is reversibly attacked with Markovnikov selectivity by another molecule of **4** to generate **2**. The Lewis acid then coordinates to the double bond of **2**, and at temperatures above 20 °C is attacked by an electron pair from the phenyl group to generate **3** via a Friedel–Crafts-type reaction with Markovnikov selectivity. Earlier attempts to observe **4** during the reaction failed, which implies an overall reaction where the rate of dimerization is faster than the rate of the elimination.[7a] An alternative mechanism has been proposed, which includes the formation of an η6-coordinated intermediate between $BiBr_3$ and the aryl groups of two molecules of the alcohol.[13] As this mechanism does not involve the elimination product, it was worthwhile to study the first step of this reaction.

An NMR tube was charged with $BiBr_3$ and cooled to −78 °C. Alcohol **1**, dissolved in $CDCl_3$, was then added slowly. The NMR tube was inserted into a probe pre-cooled to −50 °C. At this temperature, signals at δ 2.28 and δ 1.60 originating from **1** were visible in the ^1H NMR spectrum. The temperature was increased by 10 °C every 30 min. At 0 °C, broad methylene signals at δ 5.20 and δ 5.52 corresponding to **4** appeared in the ^1H NMR spectrum.[14] After 30 min at 0 °C, methylene protons at δ 4.90 and δ 5.26 due to **2** were observed in the ^1H NMR spectrum in addition to the signals of **4**. It is noteworthy that 4-methyl-2,4-diphenyl-2-pentene, an isomer of **2**, was not observed in the ^1H NMR spectrum. This isomer has been reported by other groups during the dimerization of **4** and would have been detected by its characteristic chemical shift at δ 6.14, if present.[3,4] The temperature was increased to 15 °C, during which the build-up of **4** and **2** continued. After 30 min, the ratio of **1**:**4**:**2** was 7:3:90. At this temperature, no other signals were visible in the ^1H NMR spectrum. Notably, **4** was not a rapidly consumed intermediate in the reaction. When the temperature was increased to 20 °C, characteristic signals of the diastereotopic methylene protons at δ 2.29 and δ 2.52 of **3** were observed in the ^1H NMR spectrum after 20 min. It has been proposed that the formation of **2** is reversible starting from **4**.[3] As the low temperature NMR spectroscopy experiments presented above proved that **4** was stable below 20 °C, this equilibrium could easily be studied. A pure sample of **2** was mixed with an equimolar amount of $BiBr_3$ in $CDCl_3$ overnight at 10 °C. However, only starting material **2** was visible in the ^1H NMR spectrum and no trace of compound **4** was evident. According to the rule of microscopic reversibility, **4** would have been visible if the reaction was reversible.[15] Based on these results the following mechanism is proposed: alcohol **1** eliminates water in the presence of $BiBr_3$ to yield **4** which undergoes an irreversible dimerization to yield **2** (Scheme 5). At temperatures above 20 °C cyclization to **3** occurs.



Scheme 4. Originally proposed mechanism for the dimerization of **1**.



Scheme 5. Proposed reaction mechanism.

In conclusion, we have reinterpreted the reported etherification of **1** with either methanol or butanol.[9] Instead of giving unsymmetrical ethers, reaction of **1** with $BiBr_3$ generates dimeric compounds **2** or **3** or both. By controlling the temperature, high chemoselectivity can be achieved. At temperatures below 15 °C, **2** is generated as the sole product, whilst at temperatures above 20 °C indane **3** is produced. Both compounds can be synthesized selectively in good yields. The kinetic product **2** can rearrange into the thermodynamic product **3** in the presence of $BiBr_3$. The mechanism involves elimination of water to generate **4** which undergoes an irreversible dimerization following Markovnikov selectivity to yield **2**. At temperatures above 20 °C alkene **2** is irreversibly cyclized into **3**.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.018.

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10. As CCl_4 is hazardous, CH_2Cl_2 or DCE was used in subsequent reactions. Control reactions were run in CCl_4 without any difference in the outcome.
11. No dimerization occurred without $BiBr_3$.
12. Other Lewis acids such as $FeCl_3$ were active as catalysts in this transformation.
13. In the proposed mechanism, enantioenriched phenylethanol and menthol were used. See Ref. 9.
14. Broadening could be due to coordination to $BiBr_3$.
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