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# Synthesis of dibenzocyclohepta[1,2-*a*]naphthalene derivatives from phenylacetaldehyde and alkynyl benzyl alcohols *via* sequential electrophilic addition and double Friedel–Crafts reactions†

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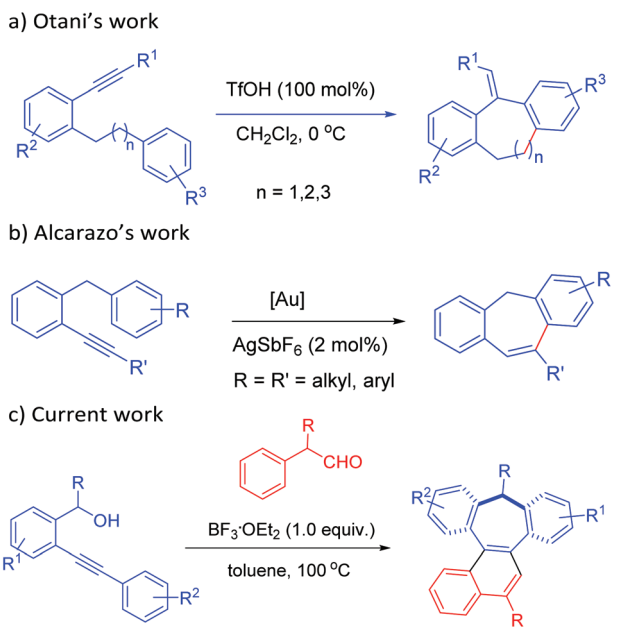
**A simple methodology has been developed for the synthesis of substituted 9*H*-dibenzo[3,4:6,7]-cyclohepta[1,2-*a*]naphthalenes from phenylacetaldehydes and *ortho*-alkynyl benzyl alcohols in the presence of a Lewis acid in moderate to good yields within a short reaction time. Interestingly, the reaction proceeds through a highly regioselective electrophilic addition followed by double Friedel–Crafts reaction to form uncommon dibenzo-fused seven-membered carbocycles.**

Carbocyclic compounds are found in many natural products and biologically active molecules.[1] These include carbocycles having a seven-membered ring, for example, ingenol is used for the topical treatment of actinic keratosis,[2] frondosins inhibit the binding of interleukin-8 (IL-8)[3] and guanacastepene has antibiotic activity.[4] Dibenzocycloheptane is an important structural motif found in many biologically active molecules.[5] For instance, allocolchicine is active against many cancer cell lines,[6] tenuifolin[7] shows antiproliferative activity against the tumor cell line DU145, and subavenoside E,[8] dibenzocycloheptadiene sihydroisosubamol,[8] and subamol[9] show inhibitory activity against α-glucosidase type IV. Similarly, substituted naphthalenes are present in many biologically important compounds[10] and optical and electronic materials[11] and constitute the backbone of many chiral ligands.[12] Although the synthesis of dibenzo-fused six-membered carbocycles is easy, the synthesis of dibenzo-fused seven- to nine-membered carbocycles is challenging due to their instability. There are a few reports on the synthesis of dibenzo-fused seven- to nine-membered carbocycles.[5e,13] The main drawback is their lengthy synthesis. The Otani group has demonstrated a methodology for the synthesis of seven- to nine-membered carbocycles *via* Brønsted acid-promoted intramolecular Friedel–Crafts-type alkenylation (Scheme 1a).[14] Very recently, Alcarazo synthesized dibenzo-fused cycloheptatrienes from 1-benzyl-2-ethynylbenzenes having a terminal and butyl substituted alkyne moiety catalysed by a gold complex (Scheme 1b).[15] Herein, we have developed a methodology for the synthesis of substituted 9*H*-dibenzo[3,4:6,7]-cyclohepta[1,2-*a*]naphthalene *via* sequential electrophilic addition and double Friedel–Crafts cyclization reactions between arylacetaldehydes and alkynyl benzyl alcohols in good yields (Scheme 1c).

In continuation of our interest in the synthesis of heterocyclic compounds using alkynes as nucleophiles,[16] we envisioned that alkyne **1a** would add to phenyl acetaldehyde (**2a**) under Lewis acidic conditions to generate vinyl carbocation **A**, which after double Friedel–Crafts reaction would give compound **3a** or **4a** (Scheme 2). Considering (2-(phenylethynyl) phenyl)methanol (**1a**) and phenyl acetaldehyde (**2a**) as model




**Scheme 1** Synthesis of dibenzocycloheptane.

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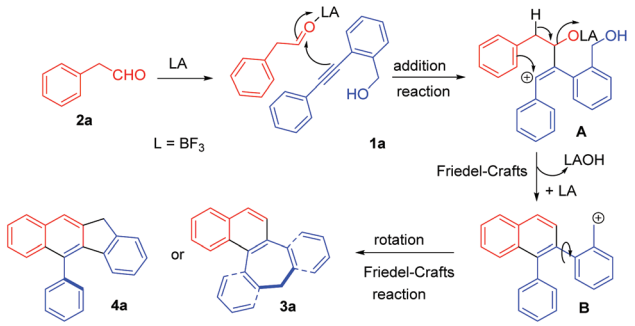
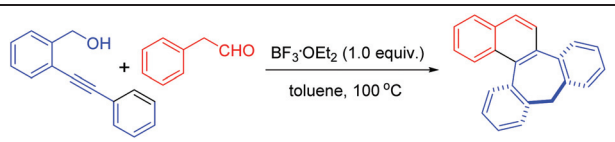



Scheme 2 Proposed reaction pathway.

substrates, the reaction was performed with ($BF_3$·$OEt_2$) (0.5 equiv.) in dichloromethane (DCM) at room temperature. To our delight, compound **3a** was obtained in 34% yield without the formation of **4a**. Encouraged by the result, the reaction was performed under different conditions as shown in Table 1. The reaction was performed in dichloroethane (DCE), acetonitrile and toluene at room temperature (entries 2–4, Table 1). Reactions in DCE and toluene gave 33% and 41% yields, respectively, whereas in acetonitrile no product was noticed. At a higher temperature such as 60 and 100 °C (entries 5 and 6, Table 1), the yield increased to 44 and 48%, respectively. After observing the effect of the temperature on the yield, the quantity of the reagent was increased from 0.5 equivalent to 1.0 equivalent (entry 7, Table 1) and it was observed that the yield increased to 70%. A higher loading of the Lewis acid of 1.5 equivalents did not improve the yield (entry 8, Table 1). Other Lewis acids such as $InCl_3$, $FeCl_3$, $In(OTf)_3$, $Sc(OTf)_3$, $Cu(OTf)_2$ and TMSOTf did not afford higher yields (entries 9–15, Table 1). Similarly, the Brønsted acids trifluoromethanesulfonic acid (TfOH) and *p*-toluenesulfonic acid (PTSA) (entries 16 and 17, Table 1) were found to be inefficient reagents for this transformation. Thus, 1 equivalent of $BF_3$·$OEt_2$ in toluene at 100 °C was found to be the optimum condition for the reaction. With these optimum reaction conditions in hand, the scope of the reaction was investigated with a variety of substrates as shown in Table 2. It is observed in Table 2 that the success of the reaction depends on the substituents in the alkyne side chain. Substrates having an electron-donating group on the aromatic ring (entries 3–6, 8–11, Table 2) gave 9*H*-dibenzo[3,4:6,7]-cyclohepta[1,2-*a*]naphthalene in moderate yields. On the other hand, a moderately electron-withdrawing group such as chlorine on the aromatic group gave a very low yield (entry 12, Table 2), which is due to the destabilization of the carbocation **A** (Scheme 3). Similarly, a strong electron-withdrawing group such as carboxylate on the aromatic ring (entry 7, Table 2) failed to give any product due to the strong destabilizing effect of the carboxylate group. On the other hand, phenylacetaldehyde gave good yields (entries 1 and 3, Table 2) compared to 2-phenyl propanaldehyde (entries 2, 4, 9–11, Table 2). *meta*-Substituted alkyne alcohol **1f** and benzo[*d*][1,3]dioxole substituted alkyne alcohol **1g** gave two regioisomeric products. It was also observed that substitution on the aromatic ring of alkyne alcohol (entries 13 and 14, Table 2) afforded the desired product with high yields, which is attributed to the enhancement of nucleophilicity of alkyne **1i**. 2,2-Diphenyl acetaldehyde, on the other hand, gave moderate yields (entries 15 and 16, Table 2). Similarly, naphthyl substituted alkyne alcohol **1j** with phenylacetaldehyde **2a** produced two products **3q** and **4q** in 35% and 45% yields, respectively. However, 2-phenylpropanal **2b** produced an inseparable mixture of **3u** and **4u** with a ratio of 2 : 3 with 84% overall yield. To our dismay, the secondary alcohol **1n** with **2b** resulted in a complex mixture. Interestingly, naphthyl substituted alkynes (entries 17 and 21, Table 2) gave high yields which might be due to the more stabilization of carbocation **A** (Scheme 3). Secondary benzylic alcohol **1k** gave a diastereomeric mixture of **3r** and **4r** with a ratio of 4 : 1 in 40% overall yield. The formation of the minor product **4r** can be explained on the basis of steric congestion between methyl and two nearby hydrogens of two phenyl rings, which are aligned in the same plane. The same is true for the formation of **3s** and **4s** as a diastereomeric mixture with a ratio of 2 : 1. In this case, the methylene group is less crowded as compared to the methyl group and therefore, the ratio increases from 4 : 1 to 2 : 1. The phenyl substituted secondary alcohol **1m** provided only a single diastereomer **3t** in 55% yield. This is because the sterically hindered phenyl group prefers the opposite side of the two adjacent aryl groups to reduce the steric repulsion. The structure of all compounds was determined with the help of $^1$H and $^{13}$C NMR and mass spectrometry. Finally, it was con-

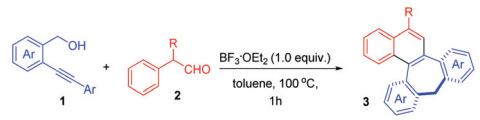
Table 1 Optimization of the reaction conditions[a]

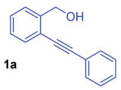
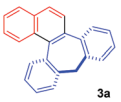
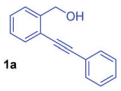
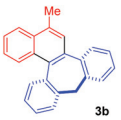
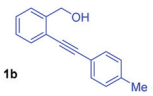
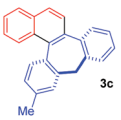
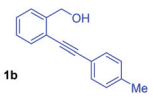
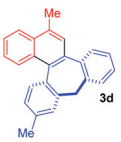
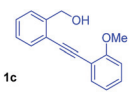
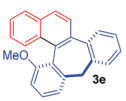
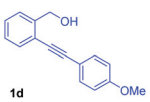
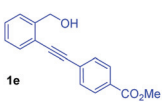
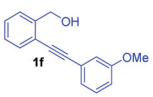
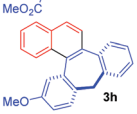
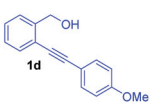
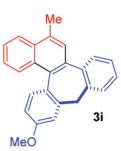



| Entry | Reagent (equiv.) | Solvent | Temp. (°C) | Time (h) | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | $BF_3$·$OEt_2$ (0.5) | DCM | rt | 1.5 | 34 |
| 2 | $BF_3$·$OEt_2$ (0.5) | DCE | rt | 2.0 | 33 |
| 3 | $BF_3$·$OEt_2$ (0.5) | $CH_3CN$ | rt | 4.0 | —[c] |
| 4 | $BF_3$·$OEt_2$ (0.5) | Toluene | rt | 1.5 | 41 |
| 5 | $BF_3$·$OEt_2$ (0.5) | Toluene | 60 | 1.5 | 44 |
| 6 | $BF_3$·$OEt_2$ (0.5) | Toluene | 100 | 0.5 | 48 |
| 7 | **$BF_3$·$OEt_2$ (1.0)** | **Toluene** | **100** | **0.5** | **70** |
| 8 | $BF_3$·$OEt_2$ (1.5) | Toluene | 100 | 0.5 | 69 |
| 9 | $InCl_3$ (0.1) | Toluene | 100 | 2.0 | 47 |
| 10 | $FeCl_3$ (0.1) | Toluene | 100 | 2.0 | 46 |
| 11 | $FeCl_3$ (0.1) | Toluene | 100 | 1.0 | 65 |
| 12 | $In(OTf)_3$ (0.1) | Toluene | 100 | 2.0 | 31 |
| 13 | $Cu(OTf)_2$ (1.2) | Toluene | 100 | 2.0 | 17 |
| 14 | $Sc(OTf)_3$ (0.2) | Toluene | 100 | 2.5 | 21 |
| 15 | TMSOTf (1.2) | Toluene | 100 | 2.0 | 29 |
| 16 | TfOH (1.2) | Toluene | 100 | 2.5 | 28 |
| 17 | PTSA (1.2) | Toluene | 100 | 3.0 | 8 |

[a] Reaction conditions: **1a** (1.0 equiv.), **2a** (1.1 equiv.). [b] Yield refers to the isolated yield. The compounds were characterised by $^1$H, $^{13}$C NMR, IR and mass spectrometry. [c] No reaction; the starting material was recovered.

**Table 2** Synthesis of 9*H*-dibenzo[3,4:6,7]-cyclohepta[1,2-*a*] naphthalene




| Entry | Alcohol **1** | Aldehyde **2** | Product **3** | Yield[a] (%) |
|---|---|---|---|---|
| 1 |  |  |  | 70 |
| 2 |  |  |  | 50 |
| 3 |  |  |  | 60 |
| 4 |  |  |  | 40 |
| 5 |  |  |  | 48 |
| 6 |  |  |  | 50 |
| 7 |  |  |  | 0[b] |
| 8 |  |  |  | 48 |
| | | |  | 29 |
| 9 |  |  |  | 48 |

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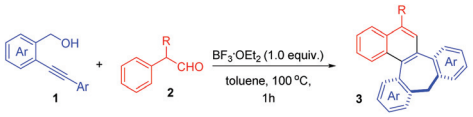


| Entry | Alcohol **1** | Aldehyde **2** | Product **3** | Yield[a] (%) |
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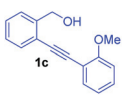
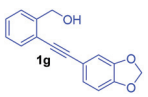
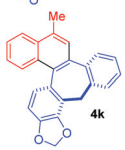
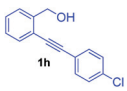
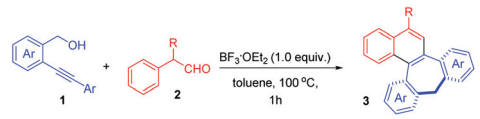
| 10 |  |  |  | 30 |
| 11 |  |  |  | 25 |
| | | |  | 15 |
| 12 |  |  |  | 15 |
| 13 |  |  |  | 85 |
| 14 |  |  |  | 78 |
| 15 |  |  |  | 40 |
| 16 |  |  |  | 48 |
| 17 |  |  |  | 35 |
| | | |  | 45 |

Table 2 *(Contd.)*




| Entry | Alcohol **1** | Aldehyde **2** | Product **3** | Yield[a] (%) |
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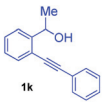
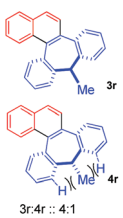
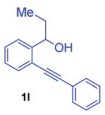
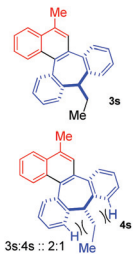
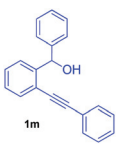
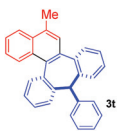
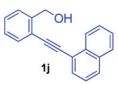
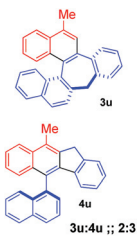
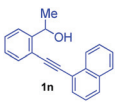
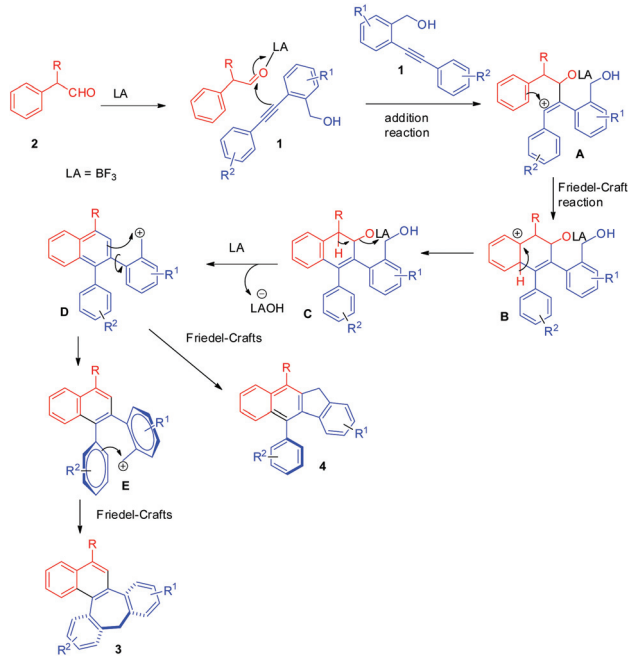
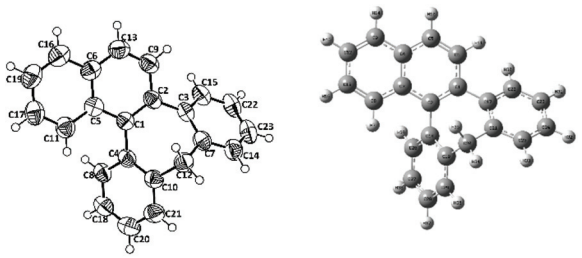
| 18 |  |  |  3r:4r :: 4:1 | 40 |
| 19 |  |  |  3s:4s :: 2:1 | 85 |
| 20 |  |  |  | 55 |
| 21 |  |  |  3u:4u ;; 2:3 | 84 |
| 22 |  |  | — | 0[c] |

[a] Yield refers to the isolated yield. The compounds were characterized by IR, NMR and mass spectrometry. [b] No reaction. The starting material was recovered in 95% yield. [c] Complex mixture.

firmed by X-ray crystallographic analysis of **3a** and **3c** and DFT calculation of compound **3a** (Fig. 1).[17] Both X-ray crystallography and DFT (DFT-B3LYP/6-31+G(d,p)) optimized structures of **3a** show a bend structure for **3a**, which is due to the repulsion among three aromatic rings attached to the cycloheptane ring. Compound **4q** is similar to a chiral biaryl compound where naphthalene and benzo[*b*]fluorene rings are in a different plane and have restricted rotation about a single bond, which is termed atropisomerism.[18] Due to the dissymmetry in molecules **3** and **4**, these compounds might have two enantiomeric forms (Fig. 2). To ascertain this, compounds **3a**, **3f**, **3q** and **4q** were subjected to HPLC analysis and it was observed that they are a mixture of equal amounts (1 : 1 ratio) of enantiomers. It may be noted that these chiral molecules are important chiral ligands in asymmetric synthesis and possess chiroptical properties.[18b,19]




Scheme 3 Plausible reaction mechanism.



**3a**

Fig. 1 X-ray crystallographic and energy-optimized structure of **3a** at the [DFT-B3LYP/6-311++G(d,p)] level of theory.

The mechanism is proposed on the basis of our findings and the previous report (Scheme 3).[20] Under Lewis acidic conditions aldehyde **2** is activated for nucleophilic attack by alkyne **1** to give intermediate **A**, which after Friedel–Crafts reaction generates intermediate **B** (Scheme 3). The intermediate **B** after aromatization and subsequent Friedel–Crafts reaction gives the final compounds **3** and **4**. In most of the cases, the reaction provided compound **3** with a seven-membered ring in the system. On the other hand, the starting material with the naphthalene derivative **1j** in the alkyne side chain gave both seven-membered **3q** and five-membered **4q** systems with **4q** in

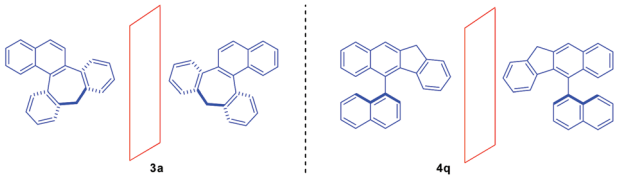
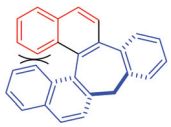



Fig. 2 Enantiomers: non-superimposable mirror images.



3q

Fig. 3 Repulsive forces experienced by two hydrogens of two naphthyl groups of **3q**.

a higher yield. This may be due to the steric repulsion between the two nearby naphthalene rings (Fig. 3). This is validated by the energy difference obtained from DFT calculations, where compound **3q** is higher in energy by almost 3.4 kcal $mol^{-1}$ compared to compound **4q**. In other words, compound **4q** is more stable than compound **3q** (see the ESI†). The reaction is highly regioselective.

In conclusion, we have developed a methodology for the synthesis of unsymmetrical 9*H*-dibenzo[3,4:6,7]-cyclohepta[1,2-*a*]naphthalene *via* sequential electrophilic addition of aldehyde to alkynes and double Friedel–Crafts cyclization reaction in moderate to good yields in a short time span. The reaction is highly regioselective and produces equal amounts of enantiomers. The reaction provides a new type of dibenzocycloheptane with an additional naphthalene ring in the molecule. The application of the synthesized compounds is under investigation.

## Conflicts of interest

There are no conflicts to declare.

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