Synthesis and Use of Versatile [1.1.1]Bicyclopentylaldehyde Building Blocks

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ABSTRACT: The [1.1.1] bicyclopentane (BCP) motif is an emerging scaffold in medicinal chemistry due to its bioisosterism to 1,4-phenylene and 1,2-alkynyl functions. Current drawback of their use is the lack of stable versatile synthetic building blocks. Aldehydes are amongst the most useful functionalities in organic chemistry. In this paper a simple one-pot procedure from aryl-halides and [1.1.1]propellane is described. Preparation of various BCP molecules is conducted to showcase the versatility of these stable intermediates.

Modern drug design increasingly facing towards 3-dimensional molecular scaffolds, as much as the chemical space within 2-dimensional has been occupied. This concept is called "escape from flatland",[1-2] and provided many interesting new scaffolds for drug discovery in recent years. Analogue based drug discovery is one of the main approaches in the delicate science of drug design.[3] The concept can benefit from the idea of bioisosteres, when two different molecules, or functional groups has very similar impact on living organisms.[4] One of the promising 3D scaffolds in this area is the [1.1.1]bicyclopentane (BCP). Over offering a novel structural motif in drug discovery, BCP has the advantage of being a promising bioisostere of 1,4-phenylene and 1,2-alkynyl functions. The utility of this functional group has been showcased on many occasions with several bioactive compounds, such as for example BCP-Darapladib, a mGlu antagonist or BCP-Tazarotene (*Figure 1*).[5-15]

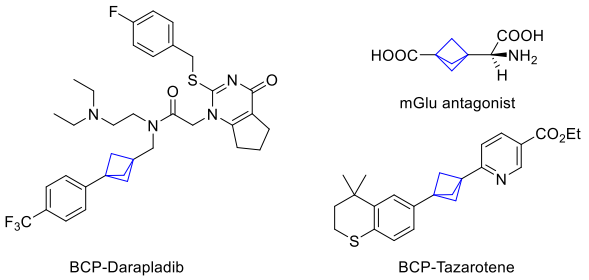
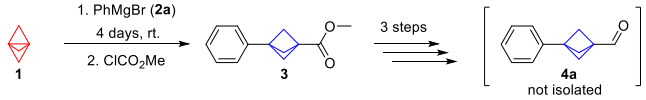


Figure 1, *Selected BCP containing bioactive molecules*

It is not surprising, that the popularity of this scaffold is increasing in industrial research, as proven by the number of patents in recent years. In contrast, their synthesis is not straightforward. The main pathway to the synthesis of this functionality is generally through [1.1.1]propellane.[16-19] However [1.1.1]propellane is not difficult to synthesize, it is not suitable for long-time storage as feedstock chemical. This interferes with the widespread application of this interesting scaffold in medicinal chemistry laboratories, therefor the existence of stabile bicyclopentane containing reagents would be highly desirable.

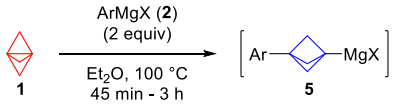
Recent developments of practical bicyclopentyl building blocks mainly involve heteroatom substituted bicyclopentanes. This might be a boronic acid derivative,[20-23] halo-substituted BCP,[24] or the useful N analogues.[25-32] A series of interesting approach was developed by Uchiyama. Upon silaboration of propellane, the resulting product has proven to be generally applicable in cross-coupling reactions.[33] Alternatively, the well-known, but fragile 1,3-diiodobicyclopentane can be encapsulated in cyclodextrins, to obtain a stable source of propellane.[34] As a carbon substituted alternative, very recently the practical large-scale synthesis of bicyclo[1.1.1]pentane-1,3-dicarboxilyc acid was solved by Mykhailiuk.[35] Synthesis of C-substituted BCP-s was investigated by the group of Walsh, leading to mono substituted [1.1.1]bicyclopentanes.[36-37]

Not surprisingly, many of the pathways to bicyclopentane containing molecules proceeds via a BCP-aldehyde intermediate,[10-15, 38-42] as aldehydes are amongst the most versatile functions in organic synthesis. In contrast the synthesis of these molecules usually involves lengthy synthesis, and no precedence of their general synthesis is showcased in the literature. These routes are usually involving oxidative-reductive pathways, as exemplified in *Scheme 1*.[40] With the available procedures it usually takes several days to obtain BCP aldehyde.



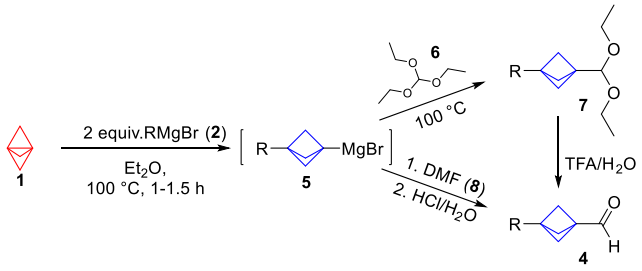
Scheme 1, Literature protocol for BCP aldehyde synthesis

Historically, the addition of Grignard reagents to the central bond of [1.1.1]propellane was known.[43-44] An important development on this field was Knochel's discovery, that in overheated Et_2O the reaction rate is several times faster, allowing the practical synthesis of BCP Grignard reagents (**5**, *Scheme 2*).[45]



Scheme 2, Knochel's advance on addition of 1 to 2

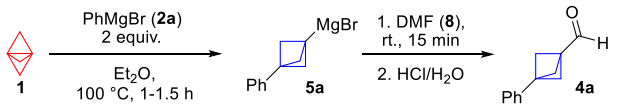
With this practical improvement, our aim was to utilize the BCP Grignard reagent in a one pot procedure for the synthesis of aldehydes. To our delight, our first experiments, with orthoformate gave the BCP ortoformate in moderate yield (**7**, *Scheme 3*). Unfortunately, it required an additional heating at 100 °C and was accompanied with inseparable by-products. Hydrolyzation of the acetal with TFA/H_2O provided the aldehyde, but the yields and purity were inconsistent throughout the experiments. Thus, we have turned our attention to the Bouveault aldehyde synthesis.[46] This process utilizes dimethylformamide (**8**) as a formyl-group source. DMF is not only conveniently accessible, also the hydrolysis upon workup provided the desired aldehyde product smoothly. This method was proceeded in just a few minutes, and eliminated the need of further heating, that might lead to degradation is some starting materials.



Scheme 3. A practical route to BCP aldehyde

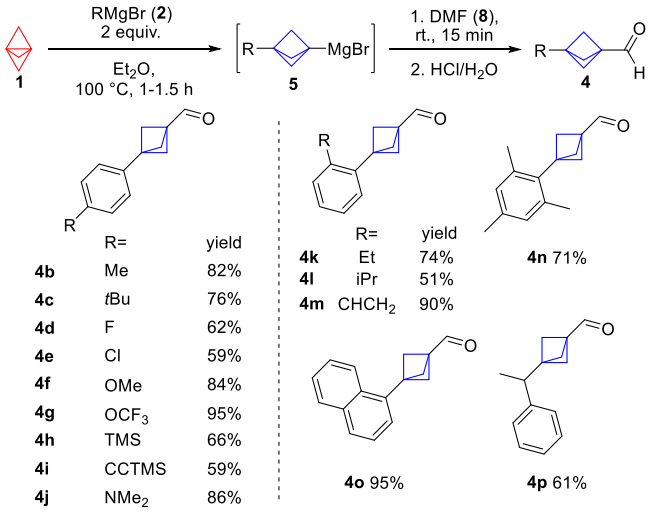
Upon optimization, we have found that Knochel's conditions proved to be reliable and robust. As working above boiling point of the solvent might be a safety issue with conventional screw-cap vials, an induction-heated reactor was used for both steps.[47] The addition of Grignard reagents to the DMF proceeded smoothly at room temperature in 15 minutes. The adduct provided the aldehyde on acidic workup.

Having a simple and fast procedure to the BCP-aldehydes we aimed to explore the versatility of the process. The two-stage procedure proved to be generally utilizable for the synthesis of various arylbicyclopentyl-aldehydes. **4a** was prepared in the induction reactor with 61% yield (*Scheme 4*). For testing the scalability of the method, 10 and 25 mmol reactions were set up in regular pressure flasks, with oil-bath heating. To our delight, the method was easily scalable and gave slightly higher yields (81 and 78%) on gram scale without the need of the special reactor.



Scheme 4, One-pot synthesis of 4a

To establish the scope of the reactions, first simple alkyl substituted products, **4b** and **4d** have been synthesized in good yields (*Scheme 5*). BCP aldehydes from dihalo substituted arenes 4-chloro- and 4-fluorobromobenzene (**4d**, **4e**), that are compatible with Grignard reagents gave desired products in moderate yields. Methoxy and trifluoromethoxy functional group containing products **4h** and **g** were synthesized in good and excellent yields. TMS and alkynyl TMS groups of **4h** and **j** might provide further possibility of transformation. Dialkylamine **4j** was synthesized in 86% yield. Sterical hindrance plays a negative role in the yield, as seen from comparing the yields of **4k** and **4l**, most likely in the step of incorporating the BCP scaffold. Smaller hindrance was not an issue, as exemplified in the case of **4n** and **4o.**

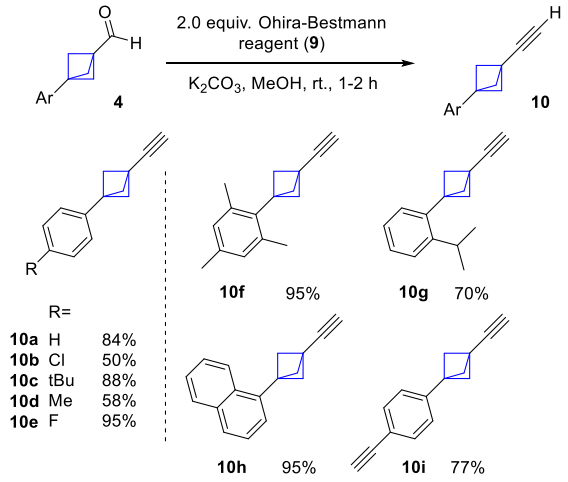


Scheme 5, Simple synthesis of BCP aldehydes. Isolated yields on 1 mmol scale.

Reactions with alkyl Grignard reagents provided products according to GCMS analysis, but the separation of these compounds from the byproducts were unsuccessful in our hands, the only exception being the phenethyl BCP (**4p**).

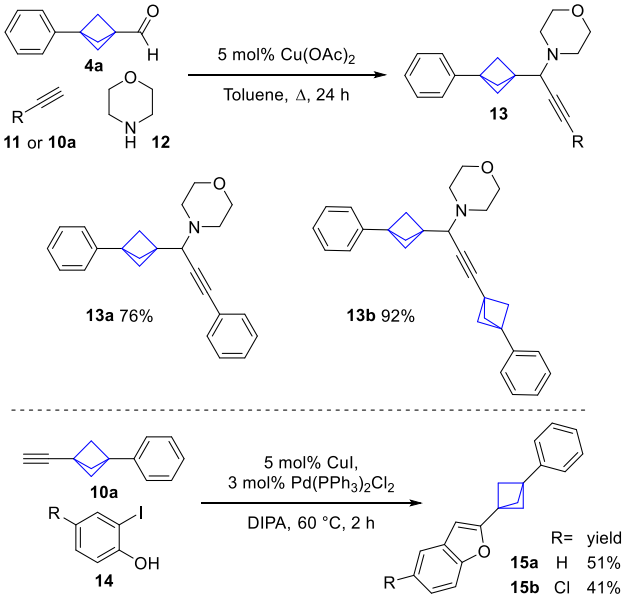
Albeit the aldehydes are known for their ability to oxidize, the BCP-aldehydes were stable in the freezer for months. After a 1-year storage, we were able to recover more than 90% of the sample mass of **4a** after column chromatography. Most of the products has a pleasant flower-like scent.

To broaden the availability of readily usable BCP containing scaffolds our aim was to synthesize alkynyl bearing bicyclopentanes, as only a few syntheses was found in the literature.[40, 48-53] This is surprising, as alkynyls are amongst the most versatile functionalities in organic chemistry. With our available BCP-aldehydes and Ohira-Bestmann reagent, terminal alkynes were obtained in good to excellent yields (*Scheme 6*).



Scheme 6, Synthesis of BCP acetylenes. Isolated yields on 0.5 mmol scale

These BCP containing building blocks allow us to gain more complexity (*Scheme 7)*. For example, through A^3 reaction[54] a simple reaction with phenylacetylene (**11**) and morpholine (**12)** provided the product **13a** in good yield. An interesting product has been obtained by reacting one of our BCP alkynes (**10a**), resulting in a double BCP containing molecule (**13b**). As further exploring the boundaries of possible molecule types, a Sonogashira-Larock type synthesis of BCP-benzofurans **15a** and **b** was achieved. To our knowledge these are the first described molecules in this class.



Scheme 7, Application of BCP aldehydes and alkynes

In conclusion, we have provided an easy access to storable, versatile [1.1.1]bicyclopentane containing building blocks, that can be converted to various molecules. We hope that this simple procedure will decrease the activation barrier for chemists to further explore the beauty of BCP chemistry and produce more useful compounds for medicinal chemistry applications and more.

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Notes

The authors declare no competing financial interest.

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