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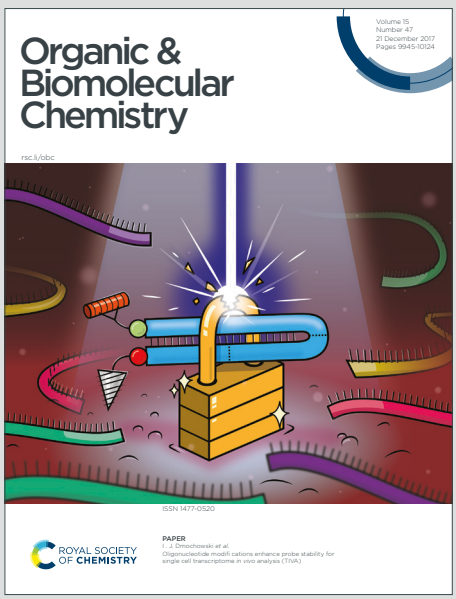

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COMMUNICATION

Rapid construction of cyclopenta[*b*]naphthalene frameworks from propargylic alcohol tethered methylenecyclopropanes

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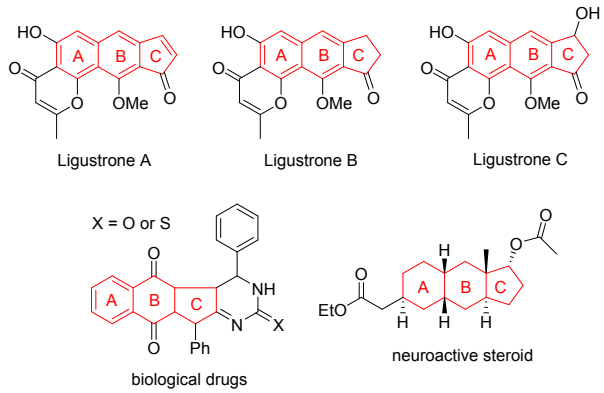
We have developed a new synthetic methodology for the rapid construction of cyclopenta[*b*]naphthalene frameworks from the reaction of propargylic alcohol tethered methylenecyclopropanes with mesyl chloride in the presence of triethylamine through cascade cyclization. The reaction can be performed under mild conditions without the use of transition metal, affording target products in moderate to good yields, and this cyclization reaction process can be enlarged to a gram scale synthesis.

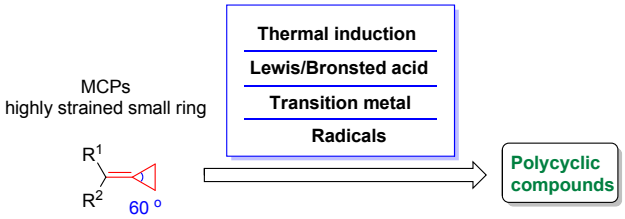
Introduction

[6,6,5] tricyclic carbon framework exists in abundant natural products,[1] bioactive molecules,[2] and functional materials[3] (Scheme 1). Especially, polyaromatic hydrocarbons (PAHs) posses semiconducting properties that permit their implementation in electronic devices.[4] Therefore, the exploration of facile and environmental-benign synthetic methods for the rapid construction of these polycyclic frameworks is highly desirable.



Scheme 1 Representative examples containing [6,6,5] tricyclic carbon frameworks.

Methylenecyclopropanes (MCPs) have been recently employed to build polycyclic motifs extensively and efficiently in consequence of the highly strained three-membered rings with distorted carbon bonds.[5] Although MCPs had high reactivity, they are in general stable at room temperature and can afford the thermodynamic driving force in organic reactions that may lead to unique and fascinating transformations under mild reactions conditions upon heating, Lewis/Brønsted acid or transition metal catalysis as well as radical reaction process,[6] presenting tremendous potential in organic synthesis (Scheme 2).



Scheme 2 Transformations of MCPs.

Thus far, many chemists have put in considerable efforts to develop efficient synthetic methods for the construction of polycyclic motifs[7] based on transition metal catalysis, photoredox catalysis, and a variety of rearrangement

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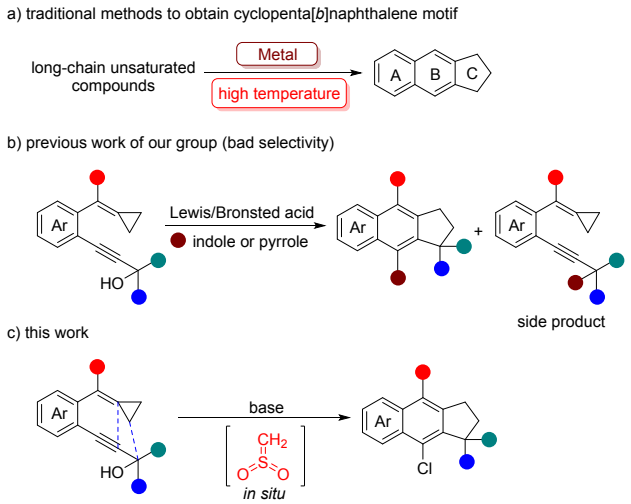
reactions. However, transition metal catalysts and high reaction temperatures (typically more than 100 °C) are usually required (Scheme 3a) to acquire cyclopenta[*b*]naphthalene structures from long-chain unsaturated compounds in most cases,[4, 8] which limited their practical applications. Recently, our group has developed a mild method to generate cyclopenta[*b*]naphthalene skeletons from propargylic alcohol tethered methylenecyclopropanes utilizing indole and pyrrole as the nucleophiles under Lewis/Brønsted acid catalysis[9] (Scheme 3b). However, a gross side product was difficult to exclude in this transformation, and the nucleophiles are only limited to indole and pyrrole, indicating a remarkable disadvantages. To solve the inadequacy, we herein wish to report a reformative protocol using methylsulfonyl chloride to *in situ* generate sulfene intermediate, which allows hydroxyl group to be a leaving group, and chloride anion behaves as the nucleophile to produce the corresponding cyclized products (Scheme 3c). These products can react with an assortment of reagents by known coupling methodologies.[10]

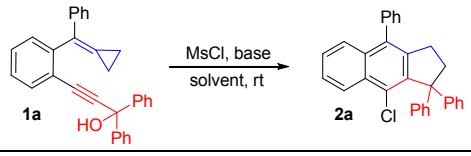


Scheme 3 Previous work and this work.

Results and discussion

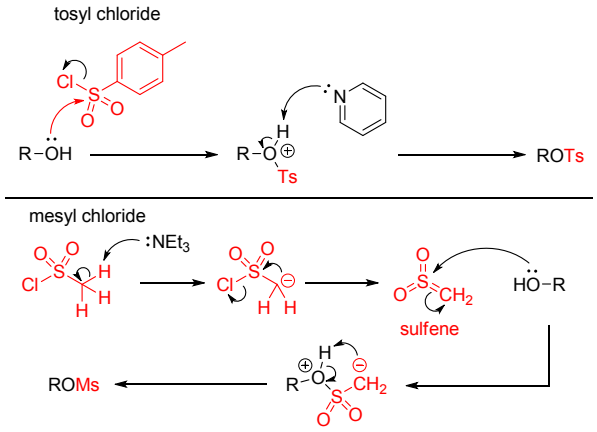
We initially used **1a** as the model substrate to inspect the reaction outcome in the presence of *para*-toluenesulfonyl chloride (TsCl) (1.5 equiv) and bases (1.6 equiv), but neither pyridine nor triethylamine could trigger the cyclization (Table 1, entries 1, 2), and **1a** could be recovered nearly completely, indicating that none of tosylated intermediates were generated. We assumed that the steric hindrance of TsCl prevented the S_N2 reaction pathway from hydroxyl group of **1a** to TsCl. Considering the different mechanisms for the combination with hydroxy group between TsCl and MsCl[11] as shown in Scheme 4, we applied MsCl for the reaction (Table 1, entry 3). To our delight, the desired cyclized product **2a** was obtained in 79% yield without the formation of side product as that in our previous work (Scheme 3b). Several other bases were tested next (Table 1, entries 4-6). Weaker organic base such as pyridine, inorganic base such as potassium carbonate, and nucleophilic base such as diisopropylamine could not facilitate the target cyclization. Then, some solvents were tested (Table 1, entries 7-9), and we found that MeCN is the best choice, providing **2a** in 84% yield. Properly increasing the equivalent of MsCl and triethylamine could make the yield of **2a** reach to 90% along with 81% isolated yield (Table 1, entries 10-12) (For more details, see the Supporting Information). The structure of **2a** was unambiguously established by X-ray diffraction. The ORTEP drawing of **2a** is shown in Fig. 1, and the corresponding CIF data are presented in the Supporting Information.

Table 1 Screening of reaction conditions



Entry	Reaction conditions[a]	Yield of **2a** [%][b]
1	TsCl (1.5 equiv), pyridine (1.6 equiv), DCM	NR
2	TsCl (1.5 equiv), Et_3N (1.6 equiv), DCM	NR
3	MsCl (1.5 equiv), Et_3N (1.6 equiv), DCM	79
4	MsCl (1.5 equiv), pyridine (1.6 equiv), DCM	NR
5	MsCl (1.5 equiv), K_2CO_3 (1.6 equiv), DCM	NR
6	MsCl (1.5 equiv), *i*-Pr_2NH (1.6 equiv), DCM	Trace
7	MsCl (1.5 equiv), Et_3N (1.6 equiv), DMSO	Trace
8	MsCl (1.5 equiv), Et_3N (1.6 equiv), MeCN	84
9	MsCl (1.5 equiv), Et_3N (1.6 equiv), THF	45
10	MsCl (2.0 equiv), Et_3N (2.1 equiv), MeCN	86
11	MsCl (2.5 equiv), Et_3N (2.6 equiv), MeCN	90
12	MsCl (3.0 equiv), Et_3N (3.1 equiv), MeCN	85
13	MsCl (2.5 equiv), Et_3N (2.6 equiv), MeCN	81[c]

[a] Reaction conditions: **1a** (0.20 mmol, 1.0 equiv), MsCl or TsCl, base, solvent, rt, for 8 h. [b] ^1H NMR yield using 1,3,5-trimethoxybenzene as an internal standard. [c] Isolated yield.



Scheme 4 Different mechanisms of combination with alcohol for TsCl and MsCl.

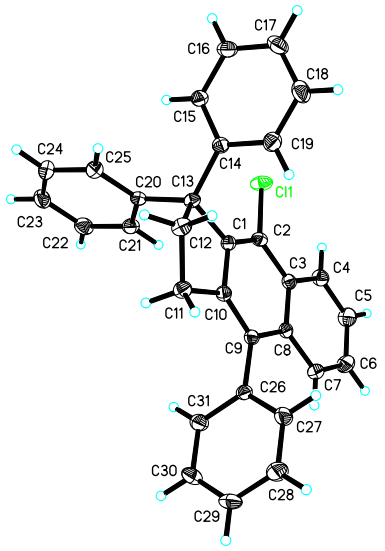
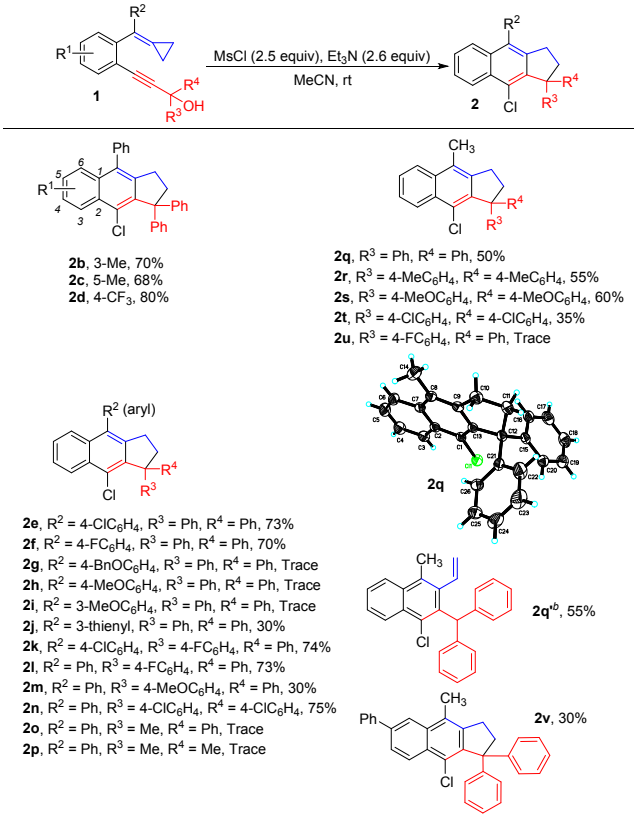


Fig. 1 X-ray structure of **2a**.

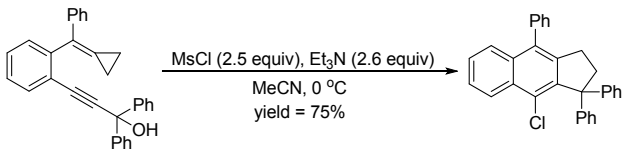
With the optimized reaction condition in hand, we subsequently evaluated diverse substrates for this cyclization (Scheme 5). When R^1 substituent was altered from H to electron-donating and electron-withdrawing groups (substrates **1b**, **1c**, **1d**), the reactions underwent smoothly, affording the desired cyclized products in high yields. Later on, we investigated the different substituent combinations of R^2, R^3, R^4. For R^2, electron-withdrawing aryls could provide the desired products in satisfying yields (products **2e**, **2f**). Conversely, when electron-donating aryls such as *p*-methoxyphenyl, *p*-benzyloxyphenyl, and 3-methoxyphenyl groups were introduced, trace of the corresponding cyclized products could be obtained (products **2g**, **2h**, **2i**), and the reaction systems became messy, which could be caused by the decomposition of the substrates or side-reactions such as Friedel-Crafts reactions due to their aromatic rings with rich electron density. When 3-thienyl was introduced to R^2 position, the target product **2j** was obtained in moderate yield. Then, we tested different substituents at R^3 and R^4 positions, and the reactions proceeded smoothly for both electron-donating and electron-withdrawing aryls, affording the desired products **2k**-**2n** in 30%-75% yields. Alkyl group placing at R^3 or R^4 position resulted in trace of cyclized products, which were caused by the elimination of intermediate **A** (See the proposed mechanism shown in Scheme 7). Thus, the corresponding alkenes were formed mainly in these cases. When R^2 was alternated to a methyl group, to our delight, the target cyclization could take place smoothly, giving **2q** in 50% yield, which was infeasible in our previous work (Scheme 3b). As we tried to lower the reaction temperature to improve the yield, interestingly, a semi-cyclized product **2q'** was obtained in 55% yield. It could be generated from intermediate **C** through 1, 4-hydrogen migration (See the proposed mechanism shown in Scheme 7). Finally, various groups at R^1, R^3 and R^4 positions with R^2 as a methyl group were investigated, furnishing the corresponding products **2r**-**2t** and **2v** in 30%-60% yields. In the case of substrate **1u**, in which R^3 was a 4-fluorobenzene moiety, the desired product **2u** was formed in trace. These results indicated that electron-donating groups were more in favor of the cyclization because electron-withdrawing groups such as fluorine atom could lower the electron density of the allenic intermediate **C** (See the proposed mechanism shown in Scheme 7), rendering that the following cyclization could not take place smoothly.



a Reaction conditions: **1** (0.2 mmol, 1.0 equiv), MsCl (0.5 mmol, 2.5 equiv), Et_3N (0.52 mmol, 2.6 equiv), MeCN (2.0 mL) at room temperture for 8 h. *b* Reaction conditions: **1** (0.2 mmol, 1.0 equiv), MsCl (0.5 mmol, 2.5 equiv), Et_3N (0.52 mmol, 2.6 equiv), MeCN (2.0 mL) at 0 °C for 8 h.

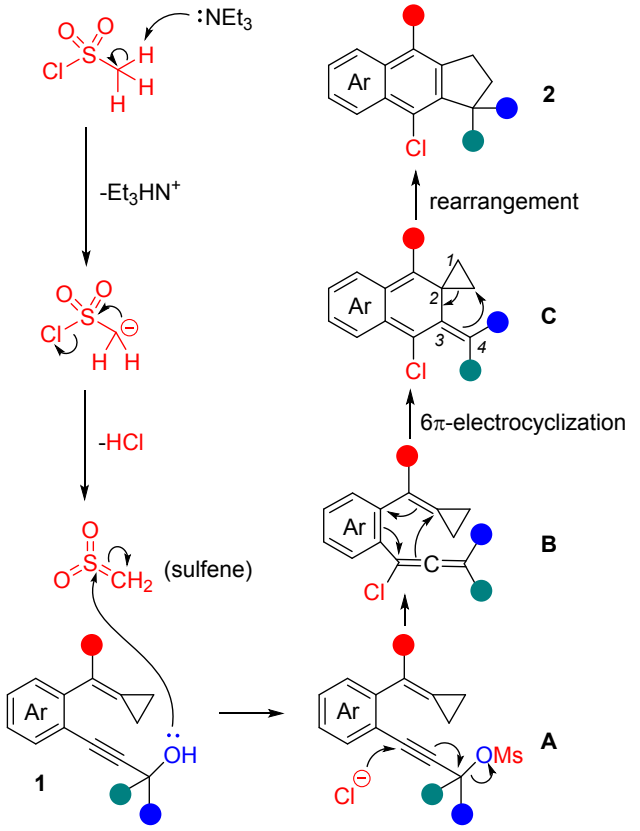
Scheme 5 Scope of substrates for the cyclization.

To further evaluate the practicability of this synthetic methodology, this reaction for **1a** was scaled to gram level at 0 °C under the standard conditions (Scheme 6). We identified that the scale enlarged reaction remained high yield, showing the synthetic potential in constructing polycyclic materials and bioactive molecules.



Scheme 6 Gram scale for the cyclization.

On the basis of these results and the previous work about methylenecyclopropanes and propargylic alcohols, a plausible mechanism for this cascade cyclization of propargylic alcohol-tethered methylenecyclopropanes is proposed in Scheme 7.[12] Firstly, the *in situ* generated sulfene from MsCl is S_N2 attacked by **1**, forming the corresponding adduct **A**. After chloride anion's nucleophilic attack, adduct **A** is transformed to allenic intermediate **B**, which could fleetly provide the product **2** after 6π-electrocyclization and the subsequent rearrangement.



Scheme 7 A plausible reaction mechanism.

Conclusions

In conclusion, we have developed a novel synthetic protocol to rapidly construct cyclopenta[*b*]naphthalene tricyclic skeletons from easily available propargylic alcohol-tethered methylidenecyclopropanes in moderate to good yields under mild conditions. In these reactions, the use of transition metal and carrying out the reaction at high temperature could be avoided, which is environment-friendly and practicable in organic synthesis. Besides, the cyclization reactions could be enlarged to gram scale, providing a useful tool for constructing the related polycyclic natural products and functional materials.

Conflicts of interest

There are no conflicts to declare.

Acknowledgment

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Rapid construction of cyclopenta[*b*]naphthalene frameworks from propargylic alcohol tethered methylenecyclopropanes

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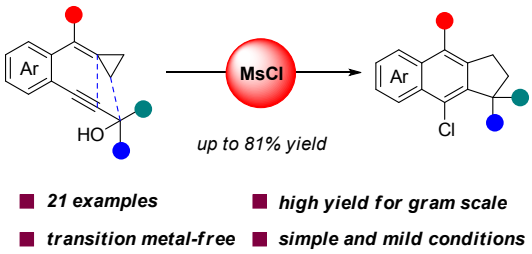
Hao-Zhao Wei,[a] Quan-Zhe Li,[a] Yin Wei,[b] and Min Shi*[a,b]



We have developed a novel synthetic methodology to rapidly construct cyclopenta[*b*]naphthalene frameworks from propargylic alcohol tethered methylenecyclopropanes and MsCl through cascade cyclization.

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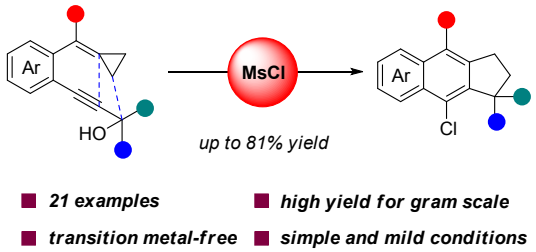

- *21 examples*
- *high yield for gram scale*
- *transition metal-free*
- *simple and mild conditions*

We have developed a novel synthetic methodology to rapidly construct cyclopenta[*b*]naphthalene frameworks from propargylic alcohol tethered methylenecyclopropanes and MsCl through cascade cyclization.