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Alder-Ene Reactions of Arynes to Form Medium-Sized and Macrocyclic Frameworks of Sizes up to a 46-Membered Ring

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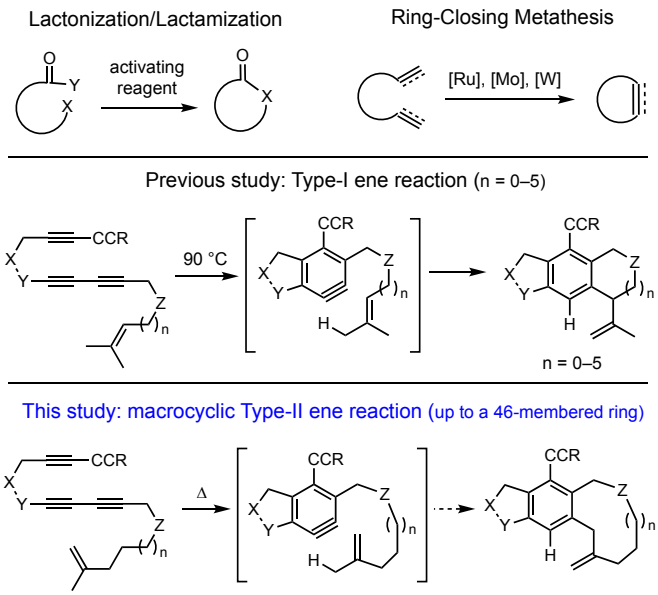
Macrocyclization via the intramolecular Alder-ene reaction of arynes to construct carbo- and hetero-macrocycles fused with indoline or isoindoline moiety is described. By installing ether, ester, alkene, and cyclic tethers at an appropriate location between the aryne and the ene donor, macrocycles up to a 46-membered ring could be constructed.

Macrocyclization is a process whereby large ring systems are constructed from acyclic precursors. It has vast applications including but not limited to the synthesis of macrocyclic natural product,[1] pharmaceuticals,[2] and organic electronic materials.[3] Thus, the invention of strategies for effective macrocyclization is of particular interest. The ring-closure of even strain-free macrocycles is challenging because of the intrinsic low effective molarity associated with the process.[4] Among various carbon-carbon and carbon-heteroatom bond-forming methods for macrocycle formation,[5–8] lactonization[6] and ring-closing metathesis[7] are the most common processes. The typical limitations of these macrocyclization strategies is a competing intermolecular reaction and relatively long reaction time. To cope with these problems, the reactions are carried out in high dilution conditions or using slow addition at elevated temperatures. Extensive studies have led to the discovery of novel catalysts and improved operation procedures to achieve high efficiency and selectivity for the synthesis of variety of macrocycles.[7b,9]

However, these optimized protocols often require extra additives, which result in increased wastes or byproducts. Thus development of more economical and environmentally benign strategies would be of significant value. In this regard, we were interested in developing macrocyclization relying on the high efficiency of the Alder-ene reaction of arynes generated via the hexadehydro Diels-Alder (HDDA) reaction.[10,11,12] The typical reaction conditions are mild and do not require any catalyst or external reagents. While studying the intramolecular Type-I Alder-ene reactions of arynes,[13] we observed the efficient formation of 8- and 10-member ring systems.[14] (Scheme 1). Encouraged by these results, we explored macrocycle formation via the Type-II Alder-ene reaction, and herein we describe the effectiveness of aryne-mediated Alder-ene reactions to form macrocycles of sizes up to a 46-membered ring.



Scheme 1. Representative macrocyclization reactions and aryne-mediate Alder-ene reaction strategies

We commenced our investigation with examining the efficiency of Type-I Alder-ene reaction to form 11- and 13-membered rings containing ether and ketal functionalities (Table 1). When a solution of ynamide-tethered tetrayne **1a** in

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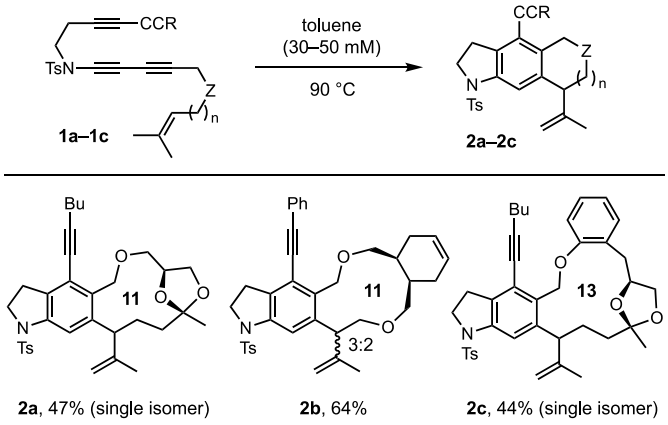

Table 1. Macrocycle formation via Type-I Alder-ene reaction. **2a** and **2c** are single diastereomers although the relative stereochemistry is not known.

toluene was heated to 90 °C, the expected 11-memberd ring product **2a** was formed as a single diastereomer in a 47% yield. On the other hand, substrate **1b** containing a *syn*-1,2-disubstituted cyclohexene linker gave **2b** as a 3:2 mixture of diastereomers in 64% yield. A single isomer of 13-membered ring product **2c** was also obtained with a 44% yield. Notably, the ketal functionality or electron-rich aromatic ring near to the aryne moiety did not interfere in the macrocycle formation.

Encouraged by these promissing aryne-mediated Type-I Alder-ene reactivity, we extended our effort to the corresponding Type-II process (Table 2). Symmetrical *bis*-1,3-diyne **3a** containing an isopropenyl ene-donor provided the expected 7-membered ring product **4a** in a 76% yield. Ynamide-tethered unsymmetrical tetraynes afforded 8-membered ring products **4b and 4c** in 56% and 60% yields. With these positive results to form medium-sized rings, we investigated the construction of larger rings. Under the standard conditions, 9–13-membered ring products were constructed with varying efficiency. The ring-size seems not to be the major determining factor for the yield. While 9–12-membered ring products **4d–4i** were isolated in the range of 34–52% yields, other 12-membered ring products **4j** and **4k** containing *syn*-1,2-substituted cyclohexene- and *cis*-alkene-containing products **4j** and **4k** were obtained in 70% and 67% yields. Interestingly, the proximal (*Z*)-alkene moiety in the tether did not interfere with the Type-II ene reaction of the distal alkene. Comparison of the yields of 12-membered ring products **4i–4K** suggests that increased rigidity of the spacer between the aryne and an ene-donor moiety improves the efficiency of the cyclization. Also, a 13-membered ring-containing product **4l** was generated in 62% yield in the absence of a functionality that rigidifies the conformation of the tether.

We further increased the length of the spacer to form macrocycles bigger than 13-membered rings (Table 3). The formation of 14-membered ring products **4m** (34%) and **4n** (53%) containing acetal and 1,2-disubstituted arene moieties in different locations of the tether showed a noticeable difference

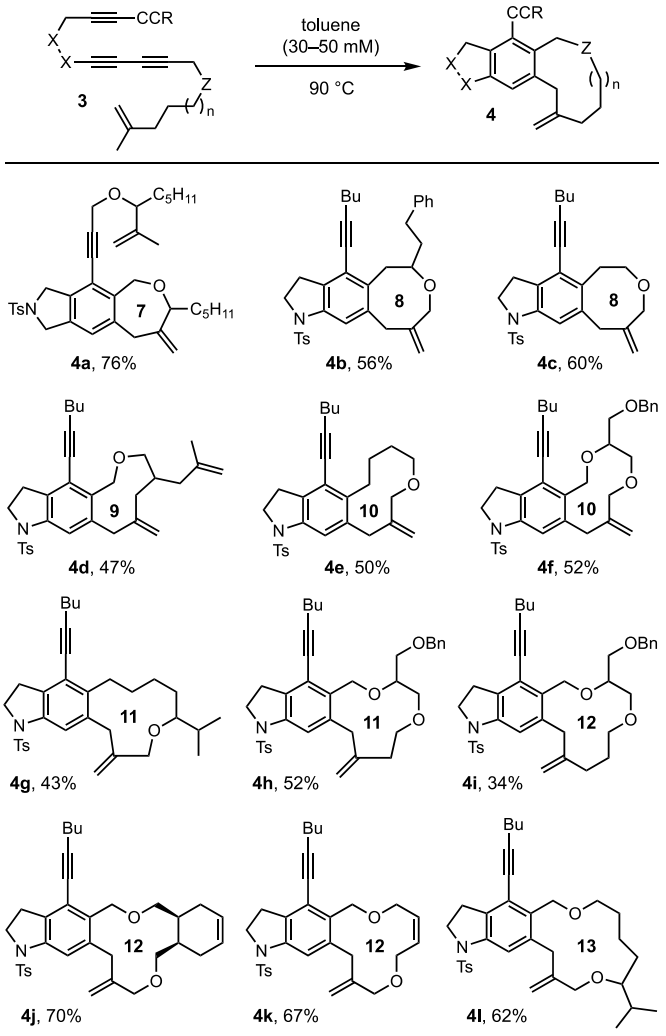

Table 2. Medium-sized and macrocyclic ring formation via Type-II Alder-ene reaction (30–50 mM concentration). The yields are the yields of isolated products.

in cyclization efficiency. Diether and arene-containing 17-membered ring product **4o** was obtained with 39% yield from a reaction running at 30–50 mM concentrations. Under more diluted conditions (4 mM), 23-membered ring product **4p** containing both ether and ester functionalities was obtained in 42% yield. The corresponding 26-, 30-, 33, and 38-membered macrolactones **4q**, **4r**, **4s**, and **4t** were obtained in 41%, 34%, 37%, and 25% yields. The yields of these macrocycles linearly decrease as the tether lengths increase. The largest macrocyclic **4u** containing a 46-membered dilactone moiety could still be obtained in about 12% yield, Although **4u** could not be isolated in its pure form, the proton NMR and mass spectroscopic data corroborate its identity. The low yield seems to be the consequence of ester-bond cleavage and oligomerization via intermolecular processes.

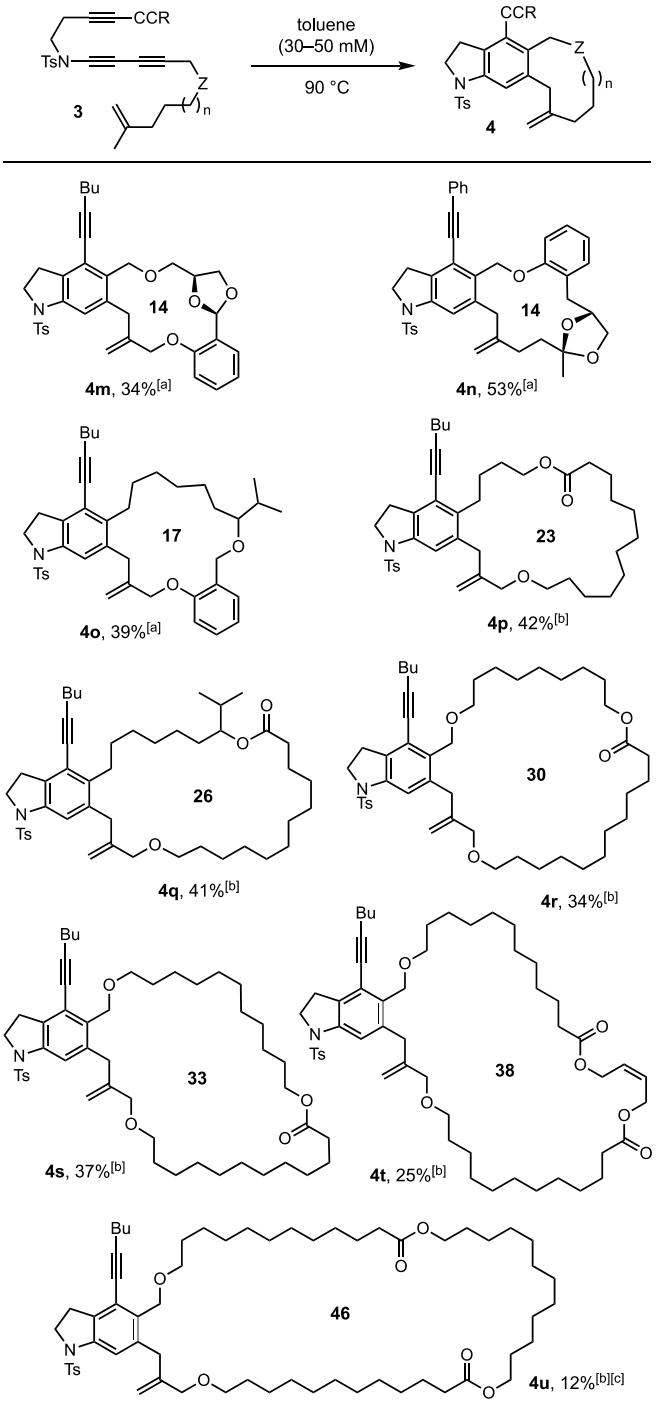

Table 3. Macrocycle formation via Type-II Alder-ene reaction. [a] Reaction in 30–50 mM concentration. [b] Reaction in 4 mM concentration. [c] The yield of compound **4u** was obtained after mutiple purifications.[15]

In conclusion, we have demonstrated that the intramolecular Type-II Alder ene reaction of aryne is a powerful tool for the construction of macrocycles. The scope of the macrocycle formation seems to be broad and the efficiency could be improved by judiciously installing functionalities that can increase the rigidity of the tether connecting the aryne and the ene-donor moieties. The yield of the macrocycle formation is inversely proportional to the size of the incipient rings, and up to a 46-membered ring could be constructed.

Author contributions

Rajdip Karmakar designed and synthesized most of the compounds **3** and **4**. Nam-Kyu Lee contributed to the preparation of **3j**, **3m, 3o, 3s**, **4j**, **4m, 4o**, and **4s**. Rajdip Karmakar, Erandi Liyanage Perera, and Daesung Lee are involved in the characterization of all the starting materials and products and the preparation of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability statement

The data supporting this article have been included as part of the Supplementary Information. The Electronic Supplementary Information (ESI) is available at https://doi.org/DOI

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15 Compound **4u** was isolated as a mixture contaminated with a minor component. In the ^{1}H NMR spectrum, the major signals correspond to compound **4u**. In contrast, the minor compound lacks aromatic protons, which is thus believed to be a product formed from the thermal decomposition of the ester tether.

Data availability statement

The data supporting this article have been included as part of the Supplementary Information. The Electronic Supplementary Information (ESI) is available at https://doi.org/DOI