An efficient synthetic method of seven- and six-membered cycloalkenes through the generation of strained cycloalkynes and following carbomagnesiation is described. Further bond formations of the resulting cycloalkenyilmagnesium intermediates with a wide variety of electrophiles enabled us to prepare diverse cycloalkene derivatives including benzoexepine analogs having a fully substituted alkene structure.

Medium-sized ring compounds are of great importance in broad research fields including pharmaceutical sciences and materials chemistry. In particular, constructing condensed medium-sized ring structures having a number of substituents is a significant and challenging issue in synthetic organic chemistry, as shown by the various bioactive arene-fused cycloheptane derivatives such as modulators for estrogen receptor (ER) (Fig. 1A).1–3 Despite the continuous efforts toward developing synthetic methodologies for condensed ring compounds, it is not easy to prepare multi-substituted fused cycloheptanes by conventional methods due to the limited cyclization methods forming a seven-membered structure.4 We herein describe an efficient method to synthesize multisubstituted cycloheptenes involving arene-fused cycloheptenes by carbomagnesiation of transiently generated strained cycloalkynes5–7 and subsequent bond formation with a variety of electrophiles.

Transformations via the carbomagnesiation of alkynes catalyzed by transition-metals such as copper and iron have been employed in tetrasubstituted alkene synthesis (Fig. 1B).8 Keeping in mind the versatility of carbomagnesiation and difficulty of cyclization to form seven-membered rings, we envisioned that a wide range of multisubstituted cycloheptenes can be prepared by the carbomagnesiation of transiently generated cycloheptynes followed by further bond formations with electrophiles on the basis of our recent achievements (Fig. 1C). Previous, we have developed an efficient cycloheptyne generation method from 2-(p-tolylsulfinyl)cycloheptenyl triflate (1a) using a phenyl Grignard reagent through sulfoxide–magnesium exchange9 followed by β-elimination, enabling us to prepare a variety of cycloheptene derivatives by cycloaddition with ynoiphiles including azides.7 The cycloalkyne generation method
from easily accessible precursors and potential electrophilicity of angle-strained cycloalkynes\(^{6,7,10}\) motivated us to develop cycloalkene synthesis through the carbomagnesiation of cycloalkynes, which is a challenging issue due to the less polar C–C triple bond and the similar nucleophilicity of the resulting alkynylmagnesium intermediates.

Considering the significance of arene-fused cycloheptene scaffolds, we first attempted the carbomagnesiation of benzene-fused cycloheptene II from sulfoxide 1b with phenylmagnesium bromide at room temperature (Fig. 2A). After quenching with aqueous ammonium chloride, benzene-fused cycloheptene 2a was obtained in high yield as a single isomer, where the regioisomer 2a' was not detected.\(^{11}\) This result clearly showed that the phenyl Grignard reagent acted both as an activator to generate cycloheptene intermediate II and as a nucleophile to form cycloheptenylmagnesium intermediate III. As no catalysts or harsh conditions were required, this transformation was promoted by the inherent reactivity of transient intermediate II with a distorted alkyne configuration.

A broad range of Grignard reagents participated in the seven- and six-membered cycloalkyne generation and following carbomagnesiation (Fig. 2B). Indeed, benzene-fused cycloheptenes 2b–2i having aryl, alkenyl, and alkyl groups were obtained in moderate to good yields with the simple procedure only by adding the corresponding Grignard reagents at room temperature without any transition-metal catalysis (Fig. 2C). Aryl Grignard reagents bearing an electron-donating or electron-withdrawing substituent at the \(p\)- or sterically hindered \(o\)-position also facilitated cycloalkyne generation and subsequent regioselective carbomagnesiation, affording benzene-fused cycloheptenes 2b–2e after protonation. In addition, benzene-fused cycloheptenes 2f–2i were also prepared using vinylmagnesium bromide and primary and secondary alkyl Grignard reagents in moderate yields.

Diverse seven- and six-membered cycloalkenes were successfully synthesized by the cycloalkyne generation and carbomagnesiation sequence (Fig. 2D). For example, treatment of benzoxepine-type cycloalkyne precursors, prepared easily from the corresponding ketones, with phenylmagnesium bromide followed by protonation selectively provided various benzoxepine derivatives 3–5 in high yields without damaging the methoxy and bromo groups. It is worth noting that the carbomagnesiation product 6 was prepared in good yield from the corresponding 2-sulfinylcycloalkenyl triflate without alkene isomerization. The reaction of a thiophene-fused cycloheptyne also proceeded smoothly to afford cycloheptene 7 in moderate yield. Furthermore, we succeeded in the generation of benzene-fused cycloheptynes and following carbomagnesiation to furnish 8–10 in low to high yields. In addition, phenylation of cyclohexyne also took place to provide \(p\)-anisyl Grignard reagents, the following protonation afforded cycloheptene 12 in moderate yield along with a small amount of diene 13 as a byproduct formed by the reaction between alkynylmagnesium intermediate IV and cycloheptyne I (Fig. 2E). These results clearly showed that a wide range of cycloalkenylmagnesium intermediates can be prepared from various cycloalkyne precursors and Grignard reagents.

Further bond-formations of the cycloheptenylmagnesium intermediate with a wide variety of electrophiles enabled the selective preparation of benzene-fused cycloheptenes 2j–2r containing fully substituted alkene scaffolds (Fig. 3). Indeed, an intermediate formed from 1b by the treatment with a phenyl...
Grignard reagent was efficiently trapped with iodine to provide iodoalkene $2j$ in high yield. The efficiency of iodination was slightly decreased when using bulky $o$-tolylmagnesium bromide in the first step. Bromination and chlorination were also accomplished by trapping N-bromosuccinimide (NBS) and $p$-toluenesulfonyl (Ts) chloride to form bromide $2l$ and chloride $2m$, respectively. Sulfanylation using thiosulfonates took place smoothly affording alkenyl sulfides $2n$ and $2o$ in good yields. Successful C–C bond formations with a variety of electrophiles such as carbon dioxide, $N,N$-dimethylformamide (DMF), and $p$-chlorobenzaldehyde were achieved to furnish tetrasubstituted alkene $2p$–$2r$ selectively. Of note, the reaction using an aldehyde only afforded ketone $2r$ probably due to the oxidation by excess aldehyde. These results clearly showed that transformations through cycloheptyne generation and carbomagnesiation enable the synthesis of cycloheptenes having a wide variety of functional groups, which are difficult to prepare by conventional methods, in a practical and simple way.

Accessible cycloalkenes were remarkably expanded by the palladium-catalyzed cross-coupling reactions (Fig. 4). For instance, the reaction between cycloheptene precursor $1b$ and phenylmagnesium bromide followed by the palladium-catalyzed Kumada–Tamao–Corriu coupling occurred smoothly, affording tetrasubstituted alkene $2s$ (Fig. 4A). Furthermore, the Mizoroki–Heck reaction between iodoalkene $2j$ and ethyl acrylate successfully provided diene $2t$ in high yield (Fig. 4B, upper). Also, alkynylation of iodide $2j$ by Sonogashira coupling resulted in the synthesis of enyne $2u$ (Fig. 4B, lower). The transformation involving palladium-catalyzed coupling allowed for the facile preparation of a benzoxepin-type selective ER$\beta$ modulator analog $14$ (Fig. 4C). Indeed, the synthesis of benzoxepine derivative $14$ possessing fluoro, $p$-hydroxyphenyl, and $p$-anisyl groups was accomplished by carbomagnesiation of cycloalkyne generated from precursor $1c$, followed by iodination and Suzuki–Miyaura cross-coupling, enabling the introduction of different aryl groups in a regioselective manner. Considering the introducible Grignard reagents and the versatility of cross-coupling chemistry, synthesizing not only the reported ER$\beta$ modulator through demethylation of the $p$-anisyl group but also diverse analogs will be realized only by changing the modules.

The utility of cycloalkene synthesis via carbomagnesiation of cycloalkynes was showcased by preparing analogs of an anti-cancer tetracyclic compound (Fig. 5). We achieved the efficient synthesis of lactone $15$ through $o$-anisylation of benzene-fused cycloheptene generated from precursor $1b$, followed by carboxylation with carbon dioxide and subsequent condensation, modifying the conditions for the preparation of cytotoxic...
compounds against cancer cells.\(^\text{16}\) Additionally, a deoxygenated analog 16 was synthesized by PPA-mediated cyclization of carboxylic acid 2p. Taking into account the difficulties to construct condensed skeletons containing a seven-membered ring and fully substituted alkenes, the present method using the convergent cycloalkene synthesis and further cyclization could enable developing bioactive compounds.

In conclusion, we have developed an efficient synthetic method of seven- and six-membered cycloalkenes through cycloalkyne generation, carbomagnesiation, and further bond formations with a wide variety of electrophiles. The carbomagnesiation of strained cycloalkynes disclosed the inherent reactivity of transiently generated cycloalkyne intermediates with a distorted alkyne configuration, which will remarkably expand the synthetic utility of cycloalkynes. Diverse arené-fused cycloheptene derivatives having a fully substituted alkenes structure such as analogs of bioactive compounds were efficiently synthesized through this reaction. Further studies to examine the preparable cycloalkenes and expand the introducible nucleophiles instead of Grignard reagents based on the good electrophilicity of transiently generated cycloalkynes clarified in this study are now ongoing.

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Conflicts of interest
There are no conflicts to declare.

Notes and references
11 Use of phenyllithium instead of phenylmagnesium bromide gave a complex mixture and phenylzene bromide did not react with 1b.
16 When we attempted a reaction using 2-(p-tolysulfinyl)-3,4-dihydro-napthohalene-1-yl triflate with 2-naphthylmagnesium bromide followed by trapping with carbon dioxide, the corresponding carboxylic acid was not obtained.