Synthesis of multisubstituted cycloalkenes through carbomagnesiation of strained cycloalkynes†

Yuya Tamura, Yasunori Minami, Yoshitake Nishiyama, Yuki Sakata, Fumika Karaki, Takamitsu Hosoya and Suguru Yoshida*

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 cycloalkenylmagnesium intermediates with a wide variety of electrophiles enabled us to prepare diverse cycloalkene derivatives including benzoepine 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 multisubstituted 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 cycloalkenes 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 cycloalkynes followed by further bond formations with electrophiles on the basis of our recent achievements (Fig. 1C).

Previously, we have developed an efficient cycloheptyne generation method from 2-(p-tolylsulfinyl)cyclohepteny 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

Fig. 1 Background and design of this study. (A) Bioactive arene-fused cycloheptane derivatives. (B) Catalytic carbomagnesiation of alkynes. (C) Concept of this work.
from easily accessible precursors and potential electrophilicity of angle-strained cycloalkynes \(^{6,7,9,10}\) 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 \(\sigma\)-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 cyclohexynes and following carbomagnesiation to furnish 8–10 in low to high yields. In addition, phenylation of cyclohexyne also took place to provide 1-phenylcyclohexene (11) in moderate yield. When cycloheptyne precursor 1a was treated with a \(p\)-anisyl Grignard reagent, 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 alkyne 2t 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 alkyne 2t 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 alkyne 2t 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 alkyne 2t 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 alkyne 2t 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 alkyne 2t 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 alkyne 2t 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 alkyne 2t 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 alkyne 2t 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 alkyne 2t 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.
compounds against cancer cells. Additionally, a deoxygenated analog was synthesized by PPA-mediated cyclization of carboxylic acid. 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 alkyn configuration, which will remarkably expand the synthetic utility of cycloalkynes. Diverse arene-fused cycloheptene derivatives having a fully substituted alkene 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.

This work was supported by JSPS KAKENHI Grant Numbers JP19K05451 (C; S. Y.), JP18H02104 (B; T. H.), and JP18H04386 (Middle Molecular Strategy; T. H.); the Naito Foundation (S. Y.); the Japan Agency for Medical Research and Development (AMED) under Grant Number JP19am0101098 (Platform Project for Supporting Drug Discovery and Life Science Research, BINDS); and the Cooperative Research Project of Research Center for Biomedical Engineering.

Conflicts of interest
There are no conflicts to declare.

Notes and references
1. (a) I. Barrett, M. J. Meegan, R. B. Hughes, M. Carr, A. J. S. Knox, N. Artemenko, G. Goliffs, D. M. Zisterer and D. G. Lloyd, Bioorg. Med. Chem., 2008, 16, 9534; (b) N. M. O’Boyle, L. M. Greene, I. Barrett, L. M. Greene, M. Carr, D. Payne, B. Twamley, A. J. S. Knox, N. O. Keely, D. M. Zisterer and M. J. Meegan, J. Med. Chem., 2018, 61, 514.
2. (a) T. Wintermantel, C. Moeller, U. Bothe, R. Nubbemeyer, L. Zorn, D. Kosemunt, A. Ter Laak, R. Bohlmann, L. Wörtmann and D. Bierer, Bayer Pharma Aktiengesellschaft, WO2011161101, 2011; (b) T. Wintermantel, C. Moeller, U. Bothe, R. Nubbemeyer, L. Zorn, A. Ter Laak, R. Bohlmann and L. Wörtmann, Bayer Intellectual Property GmbH, WO2013083568, 2013; (c) L. Zorn, D. Kosemunt, C. Möller, H. Irhaher, R. Nubbemeyer, A. Ter Laak and U. Bothe, Bayer Pharma Aktiengesellschaft, WO2015028409, 2015.
3. B. Yadagiri, U. D. Holagundu, R. Bantu, L. Nagarapu, C. G. Kumar, S. Pombala and B. Sridhar, Eur. J. Med. Chem., 2014, 79, 260.
4. For selected reviews, see: (a) J. O. Hoberg, Tetrahedron, 1998, 54, 12631; (b) T. V. Nguyen, J. M. Hartmann and D. Enders, Synthesis, 2013, 445; (c) K. T. de Oliveira, B. M. Servilha, L. C. Alves, A. L. Desiderai and T. J. Brockson, in Studies in Natural Products Chemistry, ed. A. Rahman, Elsevier, Oxford, vol. 42, 2014, pp. 421–463; (d) Y. Hu, M. Bai, Y. Yang and Q. Zhou, Org. Chem. Front., 2017, 4, 2236.
5. For selected reviews, see: (a) R. W. Hoffmann, Dehydrobenzenes and Cycloalkynes, Academic Press, New York, 1967; (b) A. Krebs and J. Wilke, Topics Current Chemistry, 1983, vol. 109, 189; (c) H. Hopf and J. Grunenberg, in Strained Hydrocarbons, ed. H. Dodziuk, Wiley-VCH, Weinheim, 2009, ch. 7; (d) C. M. Gane and E. M. Carreira, Angew. Chem., Int. Ed., 2012, 51, 3766.
6. For selected examples, see: (a) F. Scardiglia and J. D. Roberts, Tetrahedron, 1957, 1, 343; (b) G. Wittig and A. Krebs, Chem. Ber., 1961, 94, 3266; (c) F. G. Wille, Angew. Chem., Int. Ed. Engl., 1964, 3, 138; (d) W. Tochtermann, K. Oppenländer and U. Walter, Chem. Ber., 1964, 97, 1318; (e) W. Tochtermann, K. Oppenländer and U. Walter, Chem. Ber., 1964, 97, 1329; (f) R. Breslow, L. J. Altman, A. Krebs, E. Mohaisi, I. Murata, R. A. Peterson and J. Posner, J. Am. Chem. Soc., 1965, 87, 1326; (g) N. Atanes, S. Escudero, D. Pérez, E. Guiñá and L. Castedo, Tetrahedron Lett., 1998, 39, 3039; (h) M. Fujita, Y. Sakamish, M. Nishii and T. Okuyama, J. Org. Chem., 2002, 67, 8138; (i) C. M. Gane and E. M. Carreira, Chem. – Eur. J., 2002, 8, 15761; (j) J. M. Medina, T. C. McMahom, G. Jiménez-Ovies, K. N. Houk and N. K. G. Karg, J. Am. Chem. Soc., 2014, 136, 14706; (k) S. F. Tiais and R. L. Danheiser, J. Am. Chem. Soc., 2014, 136, 15489; (l) T. K. Shah, J. M. Medina and N. K. G. J. Am. Chem. Soc., 2016, 138, 4948; (m) Y. Hioki, K. Okano and A. Mori, Chem. Commun., 2017, 53, 2614; (n) V. Chari, F. M. Ippolitti and N. K. G. J. Org. Chem., 2019, 84, 3652; (o) Y. Hioki, T. Yukioka, K. Okano and A. Mori, Asian J. Org. Chem., 2018, 7, 1298; (p) E. R. Darzi, J. S. Barber and N. K. G. Angew. Chem., Int. Ed., 2019, 58, 9419; (q) R. Nakaura, K. Inoue, K. Okano and A. Mori, Synthesis, 2019, 2019, 1561; (r) Y. Hioki, A. Mori and K. Okano, Tetrahedron, 2020, 76, 131103.
7. S. Yoshida, F. Karaki, K. Uchida and T. Hosoya, Chem. Commun., 2015, 51, 8745.
8. For selected reviews, see: (a) K. Murakami and H. Yorimitsu, Beilstein J. Org. Chem., 2013, 9, 278; (b) D. S. Müller and I. Marek, Chem. Soc. Rev., 2016, 45, 4552.
9. For selected examples, see: (a) N. Furukawa, T. Shibutani and H. Fujihara, Tetrahedron Lett., 1987, 28, 2727; (b) L. Melzig, C. B. Rauhut, N. Naredi-Rainer and P. Knochel, Chem. – Eur. J., 2011, 17, 5362; (c) S. Yoshida, K. Uchida and T. Hosoya, Chem. Lett., 2014, 43, 116; (d) S. Yoshida, K. Uchida and T. Hosoya, Chem. Lett., 2015, 44, 691; (e) T. Kimura, H. Momochi, K. Moriuchi, T. Katagiri and T. Satoh, Tetrahedron Lett., 2017, 58, 3505.
10. J.-A. García-López and M. F. Greaney, Chem. Soc. Rev., 2016, 45, 6766.
11. Use of phenylithium instead of phenylmagnesium bromide gave a complex mixture and phenylzine bromide did not react with 1b.
12. F. Chemla, I. Marek and J.-F. Normant, Synlett, 1993, 665; (b) W. Lin, O. Baron and P. Knochel, Org. Lett., 2006, 8, 5673
13. P. Mampuys, C. R. McElroy, J. H. Clark, R. V. A. Orru and B. U. W. Macs, Adv. Synth. Catal., 2020, 362, 3.
14. R. J. Kloepting, A. Krasovskij and P. Knochel, Chem. – Eur. J., 2007, 13, 215.
15. For recent reviews, see: (a) R. Chinchilla and C. Nájera, Chem. Soc. Rev., 2011, 40, 5084; (b) S. Jagtap, Catalysts, 2017, 7, 267; (c) M. M. Heravi, V. Zadserjan, P. Hajibabasi and H. Hamidi, Monatsh. Chem., 2019, 150, 535; (d) S. E. Hooshmand, B. Heidari, R. Sedghi and R. S. Varma, Green Chem., 2019, 21, 381.
16. When we attempted a reaction using 2-(p-tolylsulfonyl)-3,4-dihydro- naphthalen-1-yl triflate with 2-naphthylmagnesium bromide followed by trapping with carbon dioxide, the corresponding carboxylic acid was not obtained.