



Generation of cycloalkynes through deprotonation of cyclic enol triflates with magnesium bisamides

Hioki, Yuto
Okano, Kentaro
Mori, Atsunori

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Yuto Hioki, Kentaro Okano,* and Atsunori Mori

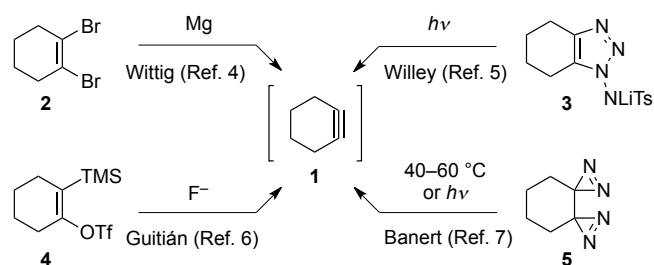
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Deprotonative generation of cyclohexynes, cycloheptynes, and cyclooctynes was achieved by controlling the reactivities of transient anionic species from corresponding enol triflates with magnesium bis(2,2,6,6-tetramethylpiperidide) as a base. The starting enol triflates are readily obtained through triflation of the corresponding ketones, allowing direct access to the cycloalkynes.

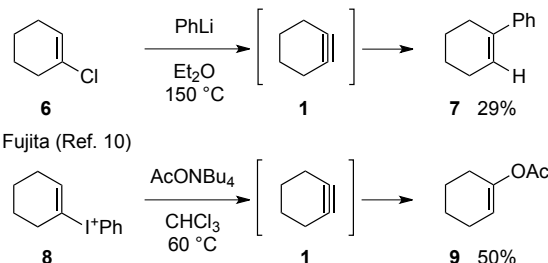
Strained organic molecules have high reactivities and various reaction modes and therefore attract much attention for synthetic use.¹ Representative arynes² and cycloalkynes³ have been extensively investigated. There are fewer reports in the literature of strained cycloalkynes than of eight-membered or larger cycloalkynes. Several methods have been used for cycloalkyne generation but the reaction conditions are harsh, or multi-step substrate preparation is involved (Scheme 1). Wittig and co-workers accomplished the generation of cyclohexyne (**1**) from 1,2-dibromocyclohexene (**2**) and magnesium by isolation of the cycloadduct with 1,3-diphenylisobenzofuran.⁴ Willey achieved photo-induced generation of cyclohexyne (**1**) from aminotriazole **3**.⁵ Guitián and co-workers generated cyclohexyne from α -trimethylsilyl enol triflate **4** with CsF under mild conditions.⁶ Banert and co-workers developed heat- or photo-induced degradation of bis(diazirine) **5** to form **1** with evolution of nitrogen gas.⁷ Rearrangement of vinylidene carbenes also provided strained cycloalkynes.⁸ Wittig and Roberts established cyclohexyne generation from a monofunctionalized cyclohexene; treatment of 1-chlorocyclohexene (**6**) with phenyllithium gave adduct **7** in 29% yield.⁹ Fujita and co-workers employed iodonium salt **8** for the formation of **1** under heating.¹⁰ Further examples of the formation of strained cycloalkynes,¹¹ seven-membered cycloalkynes,¹² and eight-membered or larger cycloalkynes have been reported.^{4,13}

Generation of cyclohexyne from difunctionalized cyclohexene



Generation of cyclohexyne from monofunctionalized cyclohexene

Wittig and Roberts (Ref. 9)



Scheme 1 Methods for cyclohexyne formation.

To the best of our knowledge, simple deprotonation of cyclic enol triflates involving β -elimination of the triflate has not yet been achieved to generate medium sized-cycloalkynes, probably due to the undesired side reactions of highly electrophilic cycloalkyne with transient anion species. Herein we disclose that magnesium bisamide, derived from magnesium chloride and two equivalents of lithium amide, facilitates the formation of strained cycloalkyne from the corresponding ketone. These features enable direct access to cycloalkynes from ketones via cyclic enol triflates, which has been recognized as an unsolved problem in the synthetic community.

Our study began by exploring effective bases for the formation of cyclohexyne (**1**) from enol triflate **10a**. We evaluated their efficacies based on the yields of the cycloadduct **12a** from 1,3-diphenylisobenzofuran (**11**) and in

Department of Chemical Science and Engineering, Kobe University, 1-1 Rokkodai,
Nada, Kobe 657-8501, Japan. E-mail: okano@harbor.kobe-u.ac.jp;
Tel: +81 78-803-6167.

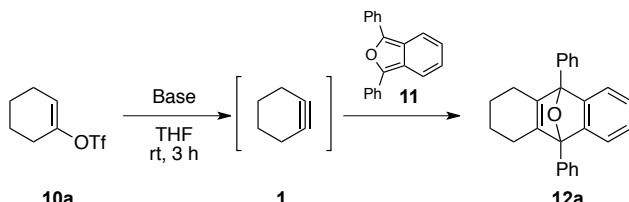
† Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data, and copies of ^1H - and ^{13}C -NMR spectra for all new compounds. See DOI: 10.1039/x0xx00000x

situ generated cyclohexyne (**1**) (Table 1). In an initial experiment, the enol triflate **10a** was treated with phenyl lithium⁹ as a base in the presence of isobenzofuran **11** (Table 1, Entry 1). All the starting triflate **10a** was consumed; however, the desired cycloadduct **12a** was not detected in the crude material, which consisted of several unidentified products due to the strong nucleophilicity of phenyl lithium, although the reaction was performed even at -78°C . We therefore examined lithium amides such as lithium diisopropylamide (LDA)¹⁴ and lithium 2,2,6,6-tetramethylpiperidide (TMP)¹⁵ (Table 1, Entries 2 and 3). The desired cycloadduct **12a** was isolated in both cases, albeit in low yields. Encouraged by the results, we then used a milder base, so-called the Knochel–Hauser base,¹⁶ TMPMgCl·LiCl (**13**), but most of the starting triflate **10a** was recovered in this case, without formation of

the desired cycloadduct **12a** (Table 1, Entry 4). Independent studies performed in Knochel's group¹⁷ and our group¹⁸ indicated that highly basic magnesium bisamides should promote deprotonation. The reaction was therefore carried out using $\text{Mg}(\text{Ni-Pr}_2)_2\cdot 2\text{LiCl}$ (**14**),^{17c,19} and an improved yield of the desired cycloadduct **12a** was obtained as we expected (Table 1, Entry 5). Unlike the case for LDA, only a small amount of **12a** was isolated, with 68% recovery of the starting triflate **10a**, when the reaction was conducted at -78°C . The sterically demanding $\text{Mg}(\text{Ni-Prt-Bu})_2\cdot 2\text{LiCl}$ (**15**) gave a lower yield of **12a** (Table 1, Entry 6). The sterically hindered amine-based magnesium bisamide $\text{Mg}(\text{Nt-Amt-Bu})_2\cdot 2\text{LiCl}$ (**16**) gave no cycloadduct **12a**, with 91% recovery of triflate **10a** (Table 1, Entry 7). We then examined cyclic amine-based magnesium bisamides. Both $\text{Mg}(\text{cis-2,6-dimethylpiperidide})_2\cdot 2\text{LiCl}$ (**17**)²⁰ and $\text{Mg}(\text{TMP})_2\cdot 2\text{LiCl}$ (**18**)¹⁷ promoted the formation of cyclohexyne (**1**) to give the cycloadduct **12a** in 51% and 56% yields, respectively (Table 1, Entries 8 and 9). We also examined zinc amides, such as $\text{Zn}(\text{TMP})_2\cdot 2\text{LiCl}$ ²¹ or $\text{TMPZnCl}\cdot\text{LiCl}$,²² but these bases did not facilitate cyclohexyne formation, and substrate **10a** was recovered (Table 1, Entries 10 and 11). We also examined the leaving group and found that the enol nonaflate was also converted to the cycloadduct **12a** in comparable yield, while cyclohexenyl chloride and bromide were recovered under the same conditions.

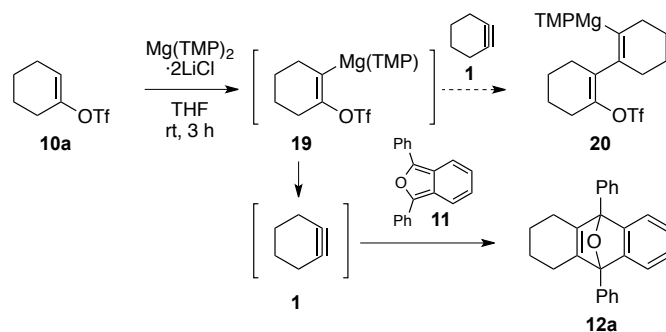
These results indicate that a magnesium bisamide is essential for achieving this transformation (Scheme 2). Unlike the case for phenyllithium,⁹ the transient anionic species **19** generated through deprotonation by $\text{Mg}(\text{TMP})_2\cdot 2\text{LiCl}$ is unreactive because of steric hindrance by the bulky TMP group attached to the magnesium ion; this hampers the undesired reaction with the cyclohexyne (**1**) yielding dimeric species **20**. The low nucleophilicity of the transient anionic species facilitates smooth generation of cyclohexyne (**1**) and subsequent cycloaddition to provide **12a**.

Table 1 Generation of cyclohexyne by deprotonation of enol triflate.



Entry	Base	Triflate 10a (%)	Cycloadduct 12a (%)
1	PhLi	<1 (trace ^d)	— ^c
2	LDA	<1 (trace ^d)	18
3	LiTMP	<1 (trace ^d)	14 (23 ^d)
4	TMPMgCl·LiCl	84	— ^c
5	$\text{Mg}(\text{Ni-Pr}_2)_2\cdot 2\text{LiCl}$	<1 (68 ^d)	38 (3 ^d)
6	$\text{Mg}(\text{Ni-Prt-Bu})_2\cdot 2\text{LiCl}$	<1	24
7	$\text{Mg}(\text{Nt-Amt-Bu})_2\cdot 2\text{LiCl}$	91	— ^c
8	$\text{Mg}(\text{DMP})_2\cdot 2\text{LiCl}$	<1	51
9	$\text{Mg}(\text{TMP})_2\cdot 2\text{LiCl}$	<1	56
10	$\text{Zn}(\text{TMP})_2\cdot 2\text{LiCl}$	84	— ^c
11	$\text{TMPZnCl}\cdot\text{LiCl}$	90	— ^c

^a The yield was determined by ^1H NMR spectrum of the crude material with 1,1,2,2-tetrachloroethane as an internal standard. ^b Reaction conditions: triflate **10a** (1 equiv; 0.50 mmol), base (3 equiv), 1,3-diphenylisobenzofuran (**11**) (1.5 equiv), THF, rt, 3 h. ^c Not detected in the crude ^1H NMR spectra. ^d Reaction temperature: -78°C . TMP = 2,2,6,6-tetramethylpiperidyl. DMP = *cis*-2,6-dimethylpiperidyl.



Scheme 2 Plausible reaction pathway: competing undesired nucleophilic addition of the transient anionic species.

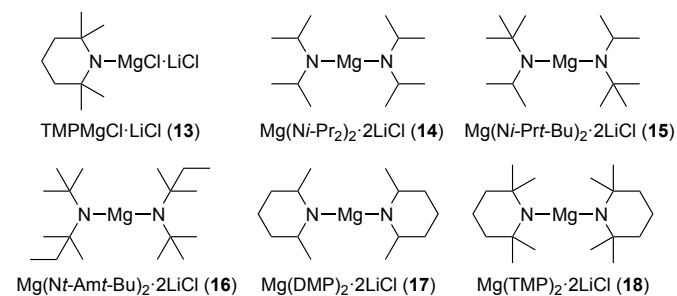
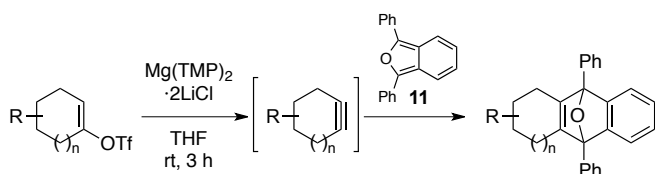
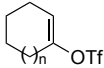
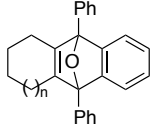
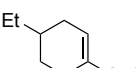
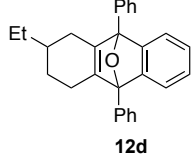
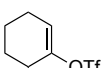
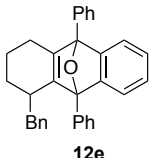
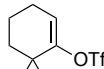
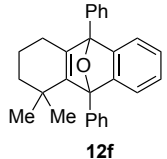
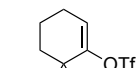
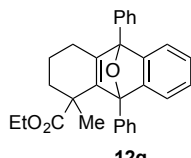
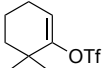
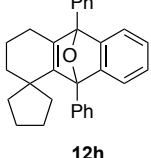
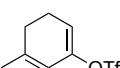
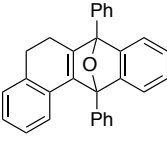


Figure 1 Structure of magnesium amides.

Having established the optimum conditions, we investigated the substrate scope of cyclic enol triflates (Table 2). Use of triflates **10b** and **10c** resulted in smooth generation of cycloheptyne and cyclooctyne, to provide the corresponding cycloadducts **12b** and **12c** in 58% and 96% yields, respectively.²³ In both cases, the cycloadduct yields were

Table 2 Substrate scope of cycloalkynes.

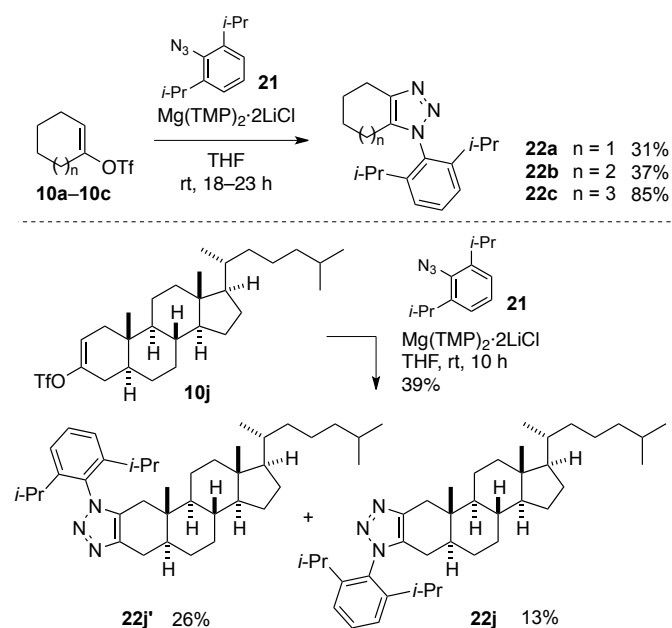


Substrate	Product	Yield (%) ^a
 10a n = 1 10b n = 2 10c n = 3	 12a–12c	55% (14% ^{b,c}) 58% (7% ^c) 96% (56% ^{b,c})
 10d	 12d	62% ^d (dr = 1:1 ^e)
 10e	 12e	65% ^f (dr = 9:4 ^e)
 10f	 12f	75% ^d
 10g	 12g	60% (dr = 3:2 ^e)
 10h	 12h	81% ^g
 10i	 12i	91%

^a Isolated yield. ^b LDA was used as a base instead of Mg(TMP)₂·2LiCl. ^c The yield was determined by ¹H NMR spectrum of the crude material with 1,1,2,2-tetrachloroethane as an internal standard. ^d Five hours. ^e The ratio of diastereomers was determined by ¹H NMR. ^f Seven hours. ^g Four hours.

significantly lower with LDA. We then investigated other six-membered cyclic enol triflates, **10d–10f**; these are readily obtained by triflation of the corresponding ketones. Treatment of enol triflate **10d** under the established conditions led to the formation of cyclohexyne bearing an ethyl group, which was converted to the desired cycloadduct **12d** in 62% yield [diastereomer ratio (dr) = 1:1, estimated using ¹H NMR spectroscopy]. Similarly, a cyclohexyne bearing a benzyl group adjacent to the alkyne moiety was converted to the corresponding adduct **12e** in 65% yield (dr = 9:4, estimated using ¹H NMR spectroscopy). The more congested substrate **10f** was also transformed to the corresponding product **12f** in 75% yield. Gratifyingly, enol triflate **10g** bearing an ester moiety was also converted to the corresponding cycloadduct **12g** in satisfactory yield (dr = 3:2, estimated using ¹H NMR spectroscopy). Spirocyclic enol triflate **10h**, which was prepared from the corresponding diol over two steps, was converted to the desired product **12h** in 81% yield. This method can be used to generate benzo-fused cyclohexyne as well as simple cyclohexynes. Enol triflate **10i**, which was derived from α-tetralone, was converted to benzo-fused cycloadduct **12i** in 91% yield.

These encouraging results prompted us to examine other reactions of cycloalkynes; however, trapping agents such as nitrones and diazo compounds gave low yields or none of the desired products.²⁴ Among the reactions we tested, strain-promoted [3+2] cycloaddition²⁵ of cycloalkynes and aryl azide **21**²⁶ proceeded smoothly (Scheme 3). The six-membered cyclic enol triflate **10a** was converted to the triazole **22a** in 31% yield. The same reaction of enol triflates **10b** and **10c** provided the corresponding product **22b** and **22c** in 37% and 85% yields, respectively.²⁷ The method was also effective for rapid access to a triazole from a complex cyclic ketone such as 5α-cholestan-3-one. Its triflate **10j** was also converted to triazole-fused cholestane derivative **22j** and **22j'** in 39% combined yield.



Scheme 3 Trapping of cycloalkynes with aryl azide.

In summary, deprotonative generation of cyclohexynes, cycloheptynes, and cyclooctynes from the corresponding enol triflates was achieved by controlling the reactivities of transient anionic species with magnesium bis(2,2,6,6-tetramethylpiperidide) as a mild base. The starting enol triflates were readily obtained by triflation of the corresponding ketones. Extension of scope and its synthetic application are currently under investigation and will be reported in due course.

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References

- (a) F. Liebman and A. Greenberg, *Chem. Rev.*, 1976, **76**, 311; (b) K. J. Shea, *Tetrahedron*, 1980, **36**, 1683; (c) M. Rubin, M. Rubina and V. Gevorgyan, *Chem. Rev.*, 2007, **107**, 3117; (d) M. Murakami and T. Matsuda, *Chem. Commun.*, 2011, **47**, 1100; (e) K. Ruhland, *Eur. J. Org. Chem.*, 2012, 2683.
- (a) H. Heaney, *Chem. Rev.*, 1962, **62**, 81; (b) M. G. Reinecke, *Tetrahedron*, 1982, **38**, 427; (c) H. Pellissier, M. Santelli, *Tetrahedron*, 2003, **59**, 701; (d) H. H. Wenk, M. Winkler, W. Sander, *Angew. Chem. Int. Ed.*, 2003, **42**, 502; (e) P. M. Tadross, B. M. Stoltz, *Chem. Rev.*, 2012, **112**, 3550.
- (a) G. Wittig, *Angew. Chem. Int. Ed. Engl.*, 1962, **1**, 415; (b) R. W. Hoffmann in *Dehydrobenzene and Cycloalkynes*, Academic Press, New York, 1967, pp. 317–361; (c) S. L. Buchwald, R. B. Nielsen, *Chem. Rev.*, 1988, **88**, 1047; (d) N. Suzuki, *Synth. Org. Chem., Jpn.*, 2007, **65**, 347; E. M. Sletten, C. R. Bertozzi, *Angew. Chem. Int. Ed.*, 2009, **48**, 6974; (e) C. M. Gampe, E. M. Carreira, *Angew. Chem. Int. Ed.*, 2012, **51**, 3766; (f) S. Yoshida, T. Hosoya, *Chem. Lett.*, 2015, **44**, 1450.
- G. Wittig, R. Pohlke, *Chem. Ber.*, 1961, **94**, 3276.
- F. G. Willey, *Angew. Chem. Int. Ed.*, 1964, **3**, 138.
- (a) N. Atanes, S. Escudero, D. Pérez, E. Guitián, L. Castedo, *Tetrahedron Lett.*, 1998, **39**, 3039; (b) W. C. Shakespeare, R. P. Johnson, *J. Am. Chem. Soc.*, 1990, **112**, 8578; (c) Y. Himeshima, T. Sonoda, H. Kobayashi, *Chem. Lett.*, 1983, 1211; (d) J. M. Medina, T. C. McMahon, G. Jimenez-Oses, K. N. Houk, N. K. Garg, *J. Am. Chem. Soc.*, 2014, **136**, 14706; (e) S. F. Tlais, R. L. Danheiser, *J. Am. Chem. Soc.*, 2014, **136**, 15489; (f) T. C. McMahon, J. M. Medina, Y.-F. Yang, B. J. Simmons, K. N. Houk, N. K. Garg, *J. Am. Chem. Soc.*, 2015, **137**, 4082; synthetic applications, (g) C. M. Gampe, S. Boulous, E. M. Carreira, *Angew. Chem. Int. Ed.*, 2010, **49**, 4092; (h) C. M. Gampe, E. M. Carreira, *Angew. Chem. Int. Ed.*, 2011, **50**, 2962; (i) C. M. Gampe, E. M. Carreira, *Chem. Eur. J.*, 2012, **18**, 15761; (j) A. S. Devlin, J. Du Bois, *Chem. Sci.*, 2013, **4**, 1059; (k) J. S. Barber, E. D. Styduhar, H. V. Pham, T. C. McMahon, K. N. Houk, N. K. Garg, *J. Am. Chem. Soc.*, 2016, **138**, 2512.
- M. Al-Omari, K. Banert, M. Hagedorn, *Angew. Chem. Int. Ed.*, 2006, **45**, 309.
- (a) K. L. Erickson, J. Wolinsky, *J. Am. Chem. Soc.*, 1965, **87**, 1142; (b) T. Harada, K. Iwazaki, T. Otani, A. Oku, *J. Org. Chem.*, 1998, **63**, 9007.
- (a) G. Wittig, G. Harborth, *Ber. Dtsch. Chem. Ges.*, 1944, **77**, 306; (b) F. Scardiglia, J. D. Roberts, *Tetrahedron*, 1957, **1**, 343; (c) L. K. Montgomery, F. Scardiglia, J. D. Roberts, *J. Am. Chem. Soc.*, 1965, **87**, 1917.
- (a) M. Fujita, Y. Sakanishi, W. H. Kim, T. Okuyama, *Chem. Lett.*, 2002, 908; (b) M. Fujita, W. H. Kim, Y. Sakanishi, K. Fujiwara, S. Hirayama, T. Okuyama, Y. Ohki, K. Tatsumi, Y. Yoshioka, *J. Am. Chem. Soc.*, 2004, **126**, 7548; (c) M. Fujita, W. H. Kim, K. Fujiwara, T. Okuyama, *J. Org. Chem.*, 2005, **70**, 480.
- Norbornyne, D. W. Laird, J. C. Gilbert, *J. Am. Chem. Soc.*, 2001, **123**, 6704.
- S. Yoshida, F. Karaki, K. Uchida, T. Hosoya, *Chem. Commun.*, 2015, **51**, 8745.
- (a) G. Wittig, H. L. Dorsch, *Justus Liebigs Ann. Chem.*, 1968, **711**, 46; (b) G. Wittig, H. L. Dorsch, J. Meske-Schuellner, *Justus Liebigs Ann. Chem.*, 1968, **711**, 55; (c) N. J. Agard, J. M. Baskin, J. A. Prescher, A. Lo, C. R. Bertozzi, *ACS Chem. Biol.*, 2006, **1**, 644; (d) H. Stoeckmann, A. A. Neves, S. Stairs, H. Ireland-Zecchini, K. M. Brindle, F. J. Leeper, *Chem. Sci.*, 2011, **2**, 932; (e) K. M. Brummond, K. D. Gesenberg, J. L. Kent and A. D. Kerekes, *Tetrahedron Lett.*, 1998, **39**, 8613; (f) N. Münster, P. Nikodemski and U. Koert, *Org. Lett.*, 2016, **18**, 4296; (g) P. J. Stang and V. Dixit, *Synthesis*, 1985, 962; (h) A. Orita, D. Hasegawa, T. Nakano, J. Otera, *Chem. Eur. J.*, 2002, **8**, 2000.
- (a) M. Hamell, R. Levine, *J. Org. Chem.*, 1950, **15**, 162; (b) R. Levine, W. C. Fernelius, *Chem. Rev.*, 1954, **54**, 449.
- (a) M. W. Rathke, R. Kow, *J. Am. Chem. Soc.*, 1972, **94**, 6854; (b) R. A. Olofson, C. M. Dougherty, *J. Am. Chem. Soc.*, 1973, **95**, 582.
- A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.*, 2006, **45**, 2958.
- (a) G. C. Clososki, C. J. Rohbogner, P. Knochel, *Angew. Chem. Int. Ed.*, 2007, **46**, 7681; (b) P. E. Eaton, C.-H. Lee, Y. Xiong, *J. Am. Chem. Soc.*, 1989, **111**, 8016; For a review, see (c) K. W. Henderson, W. J. Kerr, *Chem. Eur. J.*, 2001, **7**, 3430.
- K. Okano, H. Fujiwara, T. Noji, T. Fukuyama, H. Tokuyama, *Angew. Chem. Int. Ed.*, 2010, **49**, 5925.
- (a) Y. Joh, Y. Kotake, *Macromolecules*, 1970, **3**, 337; (b) Y. Kondo, A. Yoshida, T. Sakamoto, *J. Chem. Soc., Perkin Trans. 1*, 1996, 2331; (c) G. Lessene, R. Tripoli, P. Cazeau, C. Biran, M. Bordeaux, *Tetrahedron Lett.*, 1999, **40**, 4037.
- (a) S. A. Couper, R. E. Mulvey, D. C. Sherrington, *Eur. Polym. J.*, 1998, **34**, 1877; (b) D. R. Armstrong, J. A. Garden, A. R. Kennedy, S. M. Leenhouts, R. E. Mulvey, P. O'Keefe, C. T. O'Hara, A. Steven, *Chem. Eur. J.*, 2013, **19**, 13492.
- S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.*, 2007, **46**, 7685.
- (a) M. Mosrin, P. Knochel, *Org. Lett.*, 2009, **11**, 1837; For a recent review, see (b) B. Haag, M. Mosrin, H. Ila, V. Malakhov, P. Knochel, *Angew. Chem. Int. Ed.*, 2011, **50**, 9794.
- We have not observed a cycloadduct of cycloallene that should be generated through deprotonation of the allylic proton. Considering the almost same pK_a values of an olefinic proton and an allylic proton, it seems likely that the selectivity might be explained by the kinetic factors.
- These results might be attributed to the potential nucleophilicity of the magnesium amide or its conjugate acid (TMPH), which leads to competing nucleophilic attack to cycloalkynes.
- (a) N. J. Agard, J. A. Prescher and C. R. Bertozzi, *J. Am. Chem. Soc.*, 2004, **126**, 15046; (b) G. de Almeida, E. M. Sletten, H. Nakamura, K. K. Palaniappan and C. R. Bertozzi, *Angew. Chem. Int. Ed.*, 2012, **51**, 2443.
- S. Yoshida, A. Shiraishi, K. Kanno, T. Matsushita, K. Johmoto, H. Uekusa and T. Hosoya, *Sci. Rep.*, 2011, **1**, 82.
- For the detail of structure determination of the two isomers **22j** and **22j'**, see the Electronic Supplementary Information.