# Deprotonative Generation of Cyclohexynes from Cyclic Enol Triflates Using Aluminate Bases

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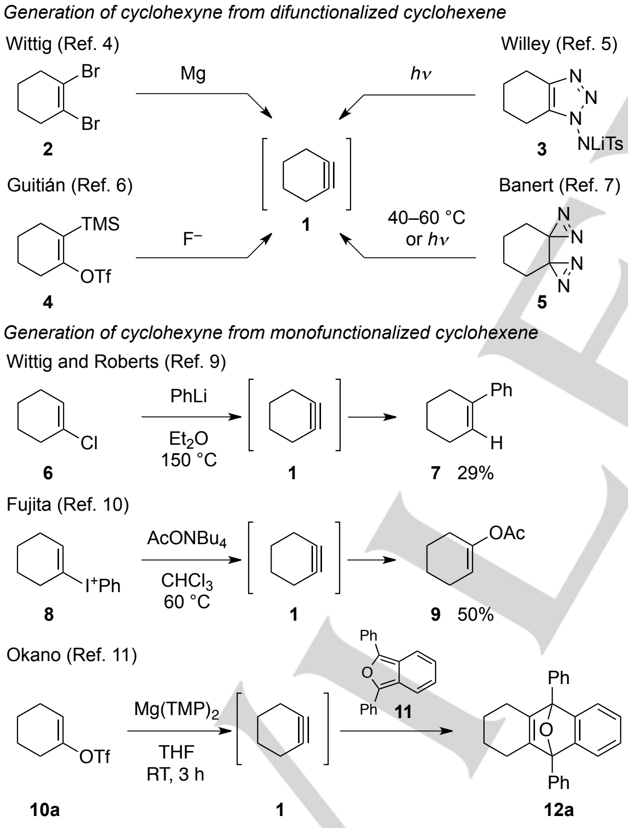
# Deprotonative Generation of Cyclohexynes from Cyclic Enol Triflates Using Aluminate Bases

Yuto Hioki, Taro Yukioka, Kentaro Okano,* and Atsunori Mori

**Abstract:** Deprotonative generation of cyclohexynes was achieved by treatment of the corresponding enol triflates with lithium triisobutyl(2,2,6,6-tetramethylpiperidino)aluminate as a base. Six-membered enol triflates involving an ester and a cyano groups were converted to the corresponding cyclohexynes at 60 °C. The reaction conditions were applied to [3+2] cycloaddition with a nitrone to form the isoxazoline.

Strained medium-sized cycloalkynes are highly reactive intermediates as well as arynes, and their generation has thus been vigorously investigated.[1] Compared to isolable cyclooctynes or larger cycloalkynes, there are fewer reports on cycloheptynes,[2] cyclohexynes, and cyclopentynes.[1i,3] These restriction is attributed to the major drawbacks such as harsh reaction conditions for generating cyclohexynes and multi-step preparation of their precursors (Scheme 1). Wittig achieved the formation of cyclohexyne (**1**) from dibromocyclohexene **2** via Grignard reagent.[4] Willey devised photolysis of aminotriazole **3**,[5] and Guitián reported the fluoride ion-promoted method using $\alpha$-trimethylsilyl enol triflate **4** as a substrate.[6] Banert also reported heat- or photo-induced degradation of bis(diazirine) **5**.[7] In addition, rearrangement of vinylidene carbenes has also been reported for the formation of strained cycloalkynes.[8] On the other hand, Wittig and Roberts utilized monofunctionalized cyclohexene **6** as a precursor for cyclohexyne (**1**).[3c,9] Fujita employed iodonium salt **8** under heating conditions.[10] Recently, our group reported generation of medium-sized cycloalkynes using Mg(TMP)$_2$· 2LiCl.[11] This method provided direct access to cycloalkynes from simple ketones via the corresponding enol triflates, but applicable ynophiles were limited. Herein, we disclose that aluminate bases, derived from trialkylaluminum and lithium 2,2,6,6-tetramethylpiperidide, promote the formation of cyclohexynes from cyclic enol triflates.

We explored suitable metal amides for generating cyclohexyne (**1**) from enol triflate **10a** (Table 1). Their efficacies



**Scheme 1.** Methods for the formation of cyclohexyne.

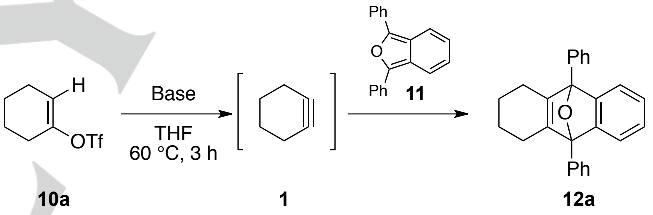


**Table 1.** Screening of bases for cyclohexyne formation[a]

| Entry | Base | Triflate **10a**[b] [%] | Cycloadduct **12a**[b] [%] |
|---|---|---|---|
| 1[c] | LiTMP | <1 | 14 |
| 2[d] | Mg(TMP)$_2$·2LiCl | <1 | 56[e] |
| 3[f] | Zn(TMP)$_2$·2LiCl·2MgCl$_2$ | 56 | –[g] |
| 4 | Et$_2$Zn(TMP)Li | <1 | 6 |
| 5 | Et$_3$Al(TMP)Li | 40 | 32 |
| 6 | *i*Bu$_3$Al(TMP)Li | <1 | 48 |

[a] Reaction conditions: triflate **10a** (1 equiv; 0.30 mmol), base (3 equiv), 1,3-diphenylisobenzofuran (**11**) (1.5 equiv), THF, 60 °C, 3 h. [b] The yield was determined by $^1$H NMR spectrum of the crude material with 1,1,2,2-tetrachloroethane as an internal standard. [c] Reaction temperature: –78 °C. [d] Room temperature. [e] Isolated yield. [f] Reaction time: 19 h. [g] Not detected in the crude $^1$H NMR spectra. TMP = 2,2,6,6-tetramethylpiperidyl.

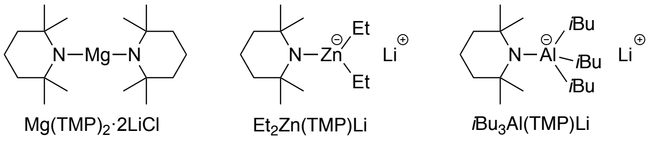


**Figure 1.** Structure of amide bases.

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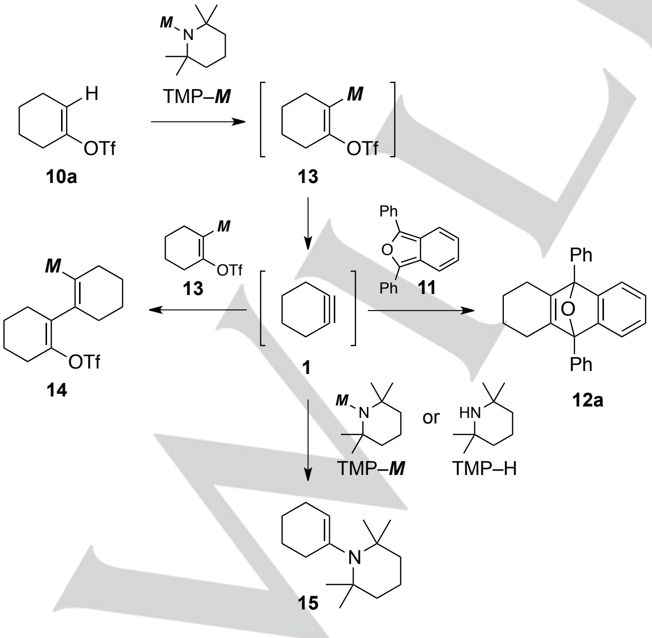
were evaluated by the yields of the cycloadduct **12a** with 1,3-diphenylisobenzofuran (**11**) and cyclohexyne (**1**), because the transient intermediate **1** is not isolable. We have reported that, among the magnesium amides, $Mg(TMP)_2{\cdot}2LiCl$[12] proved to be superior for generation of medium-sized cycloalkynes, whereas the corresponding lithium amide provided the same adduct in low yield (Entries 1 and 2).[11] We then performed the reaction with $Zn(TMP)_2{\cdot}2LiCl{\cdot}2MgCl_2$,[13] because the base was reported as a mild base. However, the desired product was not detected with 56% recovery of the starting triflate **10a** even at 60 °C for a prolonged reaction time (Entry 3). A zincate base, $Et_2Zn(TMP)Li$,[14] was used instead of the zinc bisamide in order to facilitate deprotonation of the enol triflate. As we expected, compound **10a** was consumed to give the desired cycloadduct **12a**, albeit in low yield (Entry 4). We next focused on aluminate bases, which was used for the formation of benzyne by Uchiyama and co-workers. The use of $Et_3Al(TMP)Li$[15] resulted in significant improvement of the yield of the product (Entry 5). Compared to $Et_3Al(TMP)Li$, $i\mathrm{Bu}_3Al(TMP)Li$[15,16] was superior to provide the corresponding cycloadduct in 48% yield (Entry 6).

Among the TMP bases tested, $Mg(TMP)_2{\cdot}2LiCl$ and $i\mathrm{Bu}_3Al(TMP)Li$ provided the cycloadducts in moderate yields, which demonstrates the importance of controlling the reactivities of bases or intermediates (Scheme 2). After generation of cyclohexyne (**1**) via metalated triflate **13**, undesired nucleophilic addition to **1** by the alkenyl metal species **13**, and the TMP base (TMP–***M***) or its conjugate acid (TMP–H) would provide dimeric species **14** and enamine **15**, respectively.[17] In the case of $Mg(TMP)_2{\cdot}2LiCl$ and $i\mathrm{Bu}_3Al(TMP)Li$, the transient anionic species **13** would have less nucleophilicity, because of the steric hindrance of the bulky TMP or isobutyl groups attached to the metal centers. The lower nucleophilicity of the transient anionic species preferred smooth generation of cyclohexyne (**1**) and subsequent cycloaddition to provide **12a**.



**Scheme 2.** Competing nucleophilic addition of the transient anionic species.

With the optimal aluminate base for generation of cyclohexynes determined, the scope of the reaction of triflates was examined (Table 2). Enol triflate **10b** having a benzyl group was subjected to the established conditions to give the desired cycloadduct **12b** in 33% yield (dr = 7:4). Spirocyclic enol triflate

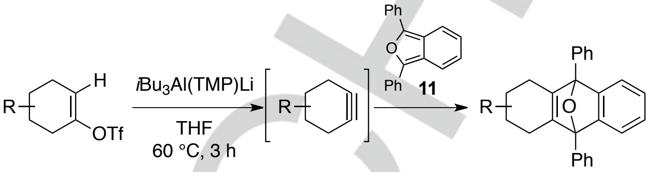
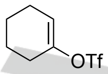
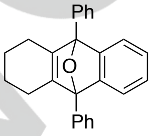
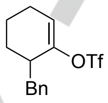
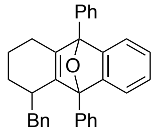
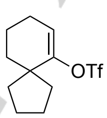
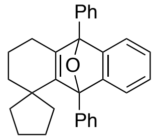
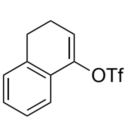
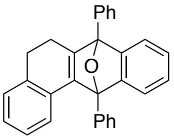
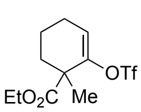
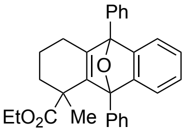
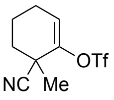
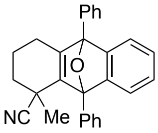


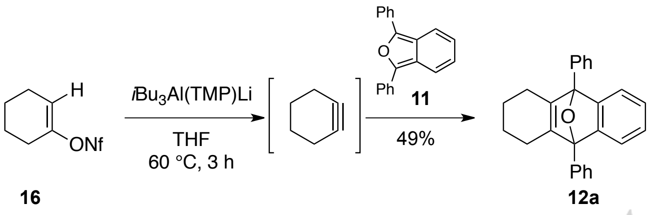
**Table 2.** Substrate scope of cycloalkynes[a]

| Triflate | Product | Yield [%][b] |
|---|---|---|
|  **10a** |  **12a** | 42 |
|  **10b** |  **12b** | 33 (dr = 7:4[c]) |
|  **10c** |  **12c** | 83 |
|  **10d** |  **12d** | 67[d] |
|  **10e** |  **12e** | 44 (dr = 1:1[c]) |
|  **10f** |  **12f** | 58 (dr = 5:3[c]) |

[a] Reaction conditions: triflate **10** (1 equiv; 0.30 mmol), base (3 equiv), 1,3-diphenylisobenzofuran (**11**) (1.5 equiv), THF, 60 °C, 3 h. [b] Isolated yield. [c] The ratio of diastereomers was determined by $^1H$ NMR. [d] The reaction was run on a 0.50-mmol scale.

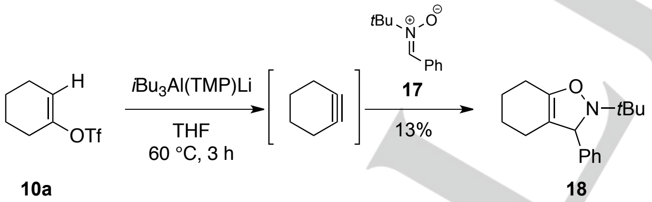
**10c** was converted to the corresponding product **12c** in 83% yield. The higher yield of the cycloadduct may be attributed to the steric effects of the spirocyclic moiety that prevent the access of these nucleophiles. Enol triflate **10d** derived from α-tetralone also generated the benzo-fused cyclohexyne to provide tetracyclic compound **12d** in 53% yield. We then investigated the tolerance of labile functional groups under the basic conditions. Enol triflate **10e** bearing an ester moiety led to the formation of the desired product **12e** in 44% yield (dr = 1:1). The nitrile group was also tolerated under the established conditions to provide cycloadduct **12f** in 58% yield (dr = 5:3).

We also performed the reaction using enol nonaflate **16** instead of enol triflate **10a** (Scheme 3). The corresponding cycloadduct was isolated in 49% with 15% recovery of the starting nonaflate. The slight increase of the yield can be rationalized by inhibition of thia-Fries rearrangement of the sulfonate.[18]



**Scheme 3.** Generation of cyclohexyne from enol nonaflate.

The aluminate base-mediated conditions were applied to [3+2] cycloaddition with N-*tert*-butyl-α-phenylnitrone (**17**)[6d] (Scheme 4). The desired isoxazoline **18** was isolated in 13% yield, whereas none of **18** was observed by $Mg(TMP)_2 \cdot 2LiCl$.



**Scheme 4.** [3+2]-Cycloaddition of cyclohexyne and nitrone.

In summary, we found that *i*Bu$_3$Al(TMP)Li was an effective base for the direct access to cycloalkynes by deprotonation of 6-membered cyclic enol triflates, which are readily prepared from the corresponding cyclohexanones. This base also allowed us to obtain the cycloadduct with the nitrone. Improvement of the reaction scope and its synthetic application are currently under investigation.

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## Conflict of interest

The authors declare no conflict of interest.

**Keywords:** strained molecules • reactive intermediates • cycloalkyne • cycloaddition • carbanions

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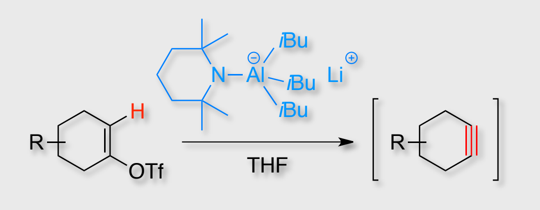
## Entry for the Table of Contents

## COMMUNICATION



Cyclohexynes are generated from the corresponding enol triflates by treatment with lithium triisobutyl(2,2,6,6-tetramethyl-piperidino)aluminate as a base. Six-membered enol triflates involving an ester and a cyano groups were converted to the corresponding cyclohexynes at 60 °C. The reaction conditions were applied to [3+2] cycloaddition with nitrone to provide the isoxazoline.

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