Ring-Expansion Reactions

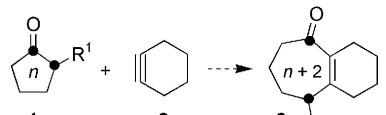
DOI: 10.1002/ange.201001137

Cyclohexyne Cycloinsertion by an Annulative Ring Expansion Cascade**

Christian M. Gampe, Samy Boulos, and Erick M. Carreira*

Dedicated to Professor John D. Roberts

Cyclohexyne has long captivated the attention of scientists and has been the focus of many theoretical and experimental studies.[1,2] The constraints of an alkyne group in a small to medium sized ring are manifested in its fleeting lifetime and correspondingly drastically enhanced reactivity. The potential application of cycloalkynes in organic synthesis has long been considered attractive. To date, the most widely employed "cycloalkyne" is 1,2-didehydrobenzene, or benzyne, which was discovered in 1942 and has recently enjoyed popularity in the context of complex molecule assembly.[3] Interestingly, the preparative use of cyclohexyne in the synthesis of useful building blocks is still lacking. Herein, we describe a direct, formal cycloinsertion reaction of cyclohexyne (**2**) into cyclic ketones **1**, to afford medium-sized, fused rings **3** (Scheme 1).



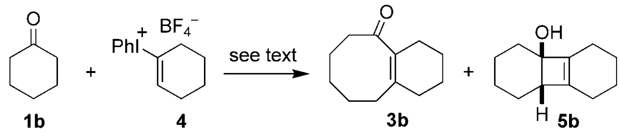
1 **2** **3**

Scheme 1. Assembly of medium-sized polycyclic carbon scaffolds by cyclohexyne insertion reactions.

Cyclohexyne was first studied and invoked as an intermediate by Roberts and Scardiglia in the substitution reaction of cyclohexenyl chloride with PhLi.[4] Attempts to generate and trap cyclohexyne (**2**) with enolates were thwarted by the conditions employed, which led to the formation of the putative 1,2-cyclohexadiene.[5] A cyclohexyne derivative could only be generated from 6,6-dimethyl-1-chlorocyclohexene, in the presence of $NaNH_2$ at 35 °C for 2 days, and trapped by enolates, albeit in 25–38 % yield.[6]

The [2+2] photocycloaddition of two olefins yields a kinetically stable cyclobutane (ring strain ca. 26 kcal mol^{-1}).[7,8] The thermal cycloaddition of small ring cycloalkyne compounds to olefins generates cyclobutenes (ring strain ca. 30 kcal mol^{-1}),[8] which undergo electrocyclic ring opening (2 minutes at 180 °C).[9] In a study involving 6,6-dimethyl-1-chlorocyclohexene as a cycloalkyne precursor and cyclohexanone enolate, it was noted that the alkoxide adduct is more prone to electrocyclic ring opening (35 °C),[6,10] in analogy to the effect seen with the oxy-Cope rearrangement.[11] In the context of several natural product synthesis projects, we became interested in examining the chemistry of cyclohexyne and cyclic ketones, their enolates or silyl enol ethers. We envisioned a strategy involving a one-pot addition/electrocyclic-ring-opening cascade. In such a process, cyclohexyne would formally insert into the ketone and generate a bicyclic ring system, with one of the rings undergoing ring expansion by two atoms. The insertion reaction of cyclopentanones would furnish bicyclo[5.4.0]undecane systems, which are found in a variety of terpenoid natural products.

The development of a general cycloinsertion reaction with cyclohexyne requires mild methods for its selective generation that prevent 1,2-cyclohexadiene formation. In this respect, Fujita and co-workers recently described facile preparation of cyclohexynes from λ^3 iodanes (**4**; Scheme 2)



1b **4** **3b** **5b**

Scheme 2. Scouting experiments for cyclohexyne insertion into **1b**.

under mild conditions at 0 °C.[12] In our scouting experiments, addition of a precooled solution of 3.0 equivalents of KO*t*Bu in tetrahydrofuran to a solution of 2.4 equivalents of iodonium **4** and cyclohexanone (**1b**) in tetrahydrofuran at −78 °C failed to give any adducts (Scheme 2). However, we noted that when the cold reaction was allowed to warm to room temperature enone **3b** was isolated in 55 % yield. The use of additives (molecular sieves, radical inhibitors) to minimize side reactions of iodonium **4** did not lead to improved yields. We speculated that under these conditions cyclohexanone (**1b**) was only partially deprotonated, thus limiting the amount of reactive species present. The use of strong amide bases (lithium diisopropylamide, lithium tetramethylpiperidide) did not lead to product formation.

[*] C. M. Gampe, S. Boulos, Prof. Dr. E. M. Carreira
Laboratorium für Organische Chemie, ETH Zürich, HCI H335
Wolfgang-Pauli-Strasse 10, 8093 Zürich (Switzerland)
Fax: (+41) 44-632-1328
E-mail: carreira@org.chem.ethz.ch
Homepage: http://www.carreira.ethz.ch

[**] This research was supported by the ETH and the Swiss National Science Foundation (200020-119838). A Kekulé scholarship was provided by the Fonds der Chemischen Industrie (to C.M.G.). We are grateful to Dr. W. B. Schweizer for the X-ray crystallographic analysis.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201001137.

A study of the deprotonation of pinacolone with hindered alkoxide bases was conducted by Brown.[13] It was noted that in the equilibrium KO*t*Bu + pinacolone ⇌ HO*t*Bu + K-pinacolonate $K_{eq} = 6.7$, whereas $K_{eq} = 57$ when $KOCEt_3$ is used. Consequently, we decided to examine the use of $KOCEt_3$ as the base in the ring-expansion reaction. Treatment of **1b** with 2.5 equivalents of $KOCEt_3$ and 1.5 equivalents of iodonium **4** afforded enone **3b** in 70% yield. Cyclobutenol **5b** was isolated as a co-product from the reaction in 6% yield. It could be shown that **5b** undergoes smooth conversion into **3b** under the conditions of the cycloinsertion reaction (KO*t*Bu, THF), implicating the cyclobutenol adduct as the primary reaction product.[14]

With these conditions in hand, the substrate scope of this ring insertion reaction was further examined (Table 1). Cyclopentanone, -hexanone, -heptanone, and -octanone underwent cycloinsertion to give fused 7-6, 8-6, 9-6 and 10-6 bicyclic ketones, respectively, in 51–76% yield (Table 1, entries 1–4). In certain cases (Table 1, entries 1, 3, 5, and 8) deconjugated enones were partially formed under the standard reaction conditions, and isomerization with NaOMe in methanol provided the corresponding conjugated isomers.[14] Cyclooctanone (**1d**; Table 1, entry 4) exclusively yielded deconjugated enone **3d** as a mixture of double bond isomers.

Having investigated simple cycloalkanones, we sought to examine more complex structures. Nopinone **1e** (Table 1, entry 5) participated smoothly in the cycloinsertion reaction to give **3e** in 74% yield. Hajos–Parrish ketone derivative **1f** provided **3f** along with a cyclobutenol, which was converted into **3f** under basic conditions at ambient temperature for a total yield of 66% (Table 1, entry 6).[14]

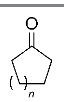
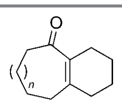
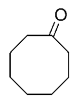
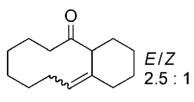
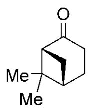
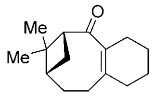
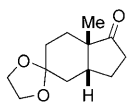
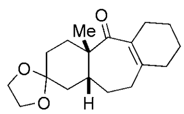
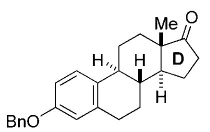
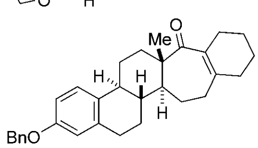
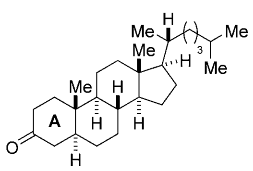
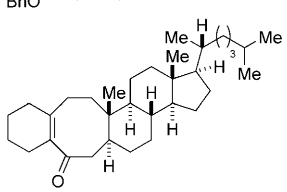
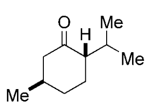
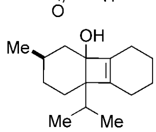
O-Benzylestrone **1g** and dihydrocholesterone **1h** (Table 1, entries 7 and 8) directly provided D- and A-ring dihomologues **3g** and **3h**, respectively. Notably, ring insertion occurs selectively into the thermodynamic enolate of **1h**.[15] The described reaction therefore enables access to unprecedented steroidal scaffolds. Menthone (**1i**; Table 1, entry 9) selectively adds **2** through the trisubstituted enolate, providing cyclobutenol **5i**, which is, however, reluctant to undergo base-induced ring opening. This result suggests that a substituent at the C4-position (*i*Pr in **5i**) halts the cascade at the stage of the cyclobutenol adduct.

Sandresolide A (**8**) as a target offers the opportunity to investigate more highly substituted and densely functionalized cyclopentanones (Scheme 3).[16] In particular, the application of the cycloinsertion strategy to sandresolide A would require the use of a C_α-methyl-substituted ketone (**6**, R^1 = Me). In this regard, the result obtained with menthone (**1i**) was of some concern.

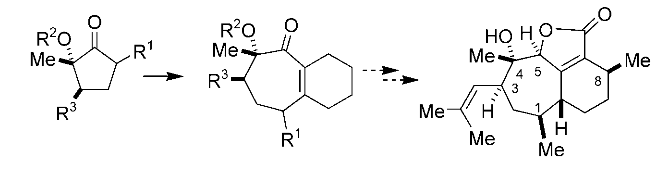
In the context of the sandresolide project, we had enol silanes **9a–b** in hand and decided to examine whether silyl enol ethers would also participate in the cycloinsertion process (Scheme 4). In the course of optimizing the reaction, we identified conditions prescribing the use of 3.0 equivalents of KO*t*Bu, 2.4 equivalents of iodonium **4**, and 1.2 equivalents of H_2O. C_α-unsubstituted enol silane **9a** underwent smooth cycloaddition to give **10a** in 76% yield.[14] As was previously observed with the unsubstituted cyclobutenols, base-induced ring-opening provided **11a**. Substrate **9b**, which incorporated a C_α-Me group, successfully engaged in the cycloaddition reaction to furnish cyclobutenol **10b** in 80% yield. As with **5i**, it did not undergo ring opening, even under forcing conditions.

We decided to target cyclobutenol adducts that contained a leaving group at the C4-position to enable fragmentation as an alternative pathway for ring opening (see **10c**).[17] However, caution might be warranted as the corresponding enolate could be susceptible to elimination to the enone under the reaction conditions.[18] Neverthe-

Table 1: Reaction of ketones (**1**) with iodonium compound **4**.[a]

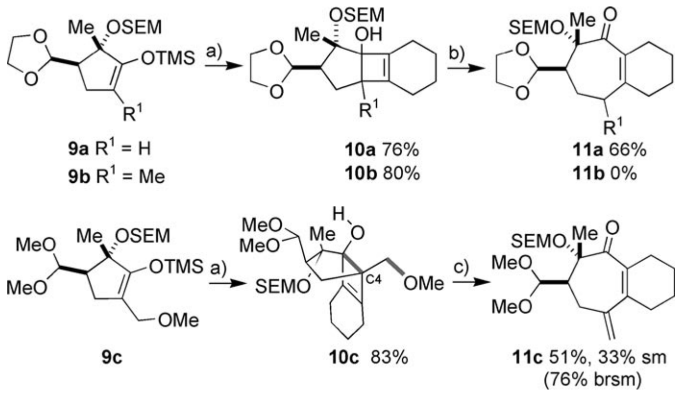
Entry		Substrate		Product	Yield [%]
1	$n=1$: **1a**		**3a**		67[b]
2	$n=2$: **1b**		**3b**		76[c]
3	$n=3$: **1c**		**3c**		64[b]
4	**1d**		**3d**		51
5	**1e**		**3e**		74[b]
6	**1f**		**3f**		66[c]
7	**1g**		**3g**		54[d]
8	**1h**		**3h**		58[b]
9	**1i**		**5i**		52

[a] Reaction conditions: ketone **1** (0.5 mmol), **4** (1.5 equiv), $KOCEt_3$ (2.5 equiv), THF (25 mL), −78 °C to RT. [b] Combined yield of **3** and its deconjugated isomer. [c] Cyclobutene adduct isolated and opened in successive step.[14] [d] 10% starting material recovered.



6 7 8

Scheme 3. C_α-substituted ketone **6** in the construction of the sandresolide (**8**) core.



Scheme 4. Cycloaddition reactions with enol ethers **9a–c**. Reagents and conditions: a) **4** (2.4 equiv), KO*t*Bu (3.0 equiv), H_2O (1.2 equiv), THF, −78 °C to RT; b) KO*t*Bu (0.5 equiv), [18]crown-6 (0.5 equiv), THF, RT; c) KHMDS (1.1 equiv), [18]crown-6 (0.5 equiv), THF, RT. KHMDS = potassium hexamethyldisilazide, SEM = 2-(trimethylsilyl)-ethoxymethyl, TMS = trimethylsilyl, sm = starting material, brsm = based on recovered starting material.

less, we were pleasantly surprised to find that when **9c** was subjected to the reaction conditions adduct **10c** was isolated in 83 % yield. Treatment of this cyclobutenol with 1.1 equivalents of KHMDS and 18-crown-6 in tetrahydrofuran at room temperature afforded **11c** in 51 % yield (76 % brsm).

We have obtained a crystal structure of **5f** and its analysis is revealing (Figure 1).[14,19] The C1–C4 single bond in the cyclobutenol is significantly stretched to 1.596 Å, as compared to 1.573 Å in a previously reported unsubstituted cyclobutene.[20] Concomitantly, the C1–O single bond is shortened by 0.022 Å, when compared to an unstrained tertiary alcohol.[21] These observations suggest a hyperconjugative interaction of the oxygen lone pair with the C1–C4 σ* orbital. This phenomenon was predicted computationally by Houk and Rondan[22a] as being pivotal for the drastically lowered activation barrier for the electrocyclic ring-opening reaction of π-donor-substituted cyclobutenes.[10,22] Therefore,

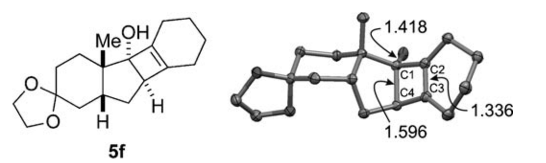
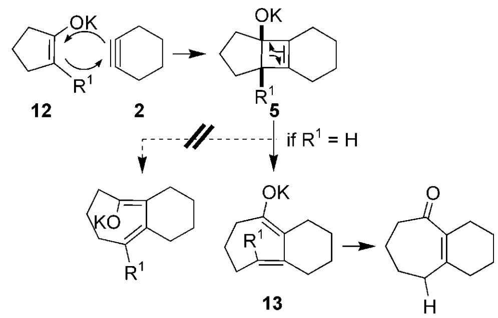


Figure 1. Representation of the crystal structure of **5f** with selected bond lengths in Ångströms (hydrogen atoms omitted for clarity). Ellipsoids set at 50 % probability.

the structure is stereoelectronically optimally set up for C1–C4 bond rupture.[23]

A detailed discussion of the reaction mechanism exceeds the scope of this communication; however, some general comments can be made. The action of alkoxide base on ketone **1** or silylenolether **9** generates enolate **12** (Scheme 5), which subsequently undergoes *syn* addition to cyclohexyne (**2**). The unsubstituted cycloadducts **5a–h** and **10a** ($R^1 = H$) undergo rapid, conrotatory, electrocyclic ring-opening. This process is facilitated by the oxy substituent, which presumably undergoes torquoselective outward rotation to give dienolate **13**.[10,22] The reluctance of certain substrates (**5i**, **10b**, $R^1 \neq H$) to undergo electrocyclic opening can be understood by the additional steric congestion that arises from either conrotatory mode.



Scheme 5. Proposed working model for the cycloalkyne insertion.

In summary, we report the first cycloinsertion reaction of cyclohexyne (**2**) into cyclic ketones. This transformation is comprised of consecutive annulation and ring-expansion reactions. Facile derivatization of cyclic structures is achieved, which enables rapid access to polycyclic medium-sized rings, from a collection of simple and more complex cyclic ketones (cycloalkanones, estrone, cholesterone, and densely functionalized cyclopentanones). The cycloadducts of unsubstituted enolates readily undergo base-induced electrocyclic ring-opening reactions. The surprising participation of a β-alkoxy enolate in the cycloaddition affords a product that is set up for ring-opening fragmentation. Interesting insight was obtained by the analysis of the structural characteristics of cyclobutenol **5f**. The X-ray crystal structure provides experimental validation for the increased reactivity of π-donor-substituted cyclobutenes, which had earlier been theorized in computational studies. The cyclohexyne insertion provides an intriguing simplifying transformation for medium-sized rings. The intermediate cyclobutenes may also find further applications as they are amenable to a host of other manipulations. Studies into the reactions of cyclohexyne and its derivatives are ongoing and will be reported in due course.

Experimental Section

General procedure: A solution of $KOCEt_3$ (1.25 mmol) in THF (5 mL) was allowed to stream down the walls of the flask over 5 minutes into a precooled (−78 °C) solution of ketone **1** (0.5 mmol) and iodonium **4** (0.75 mmol) in THF (20 mL). The mixture was stirred at −78 °C for 30 minutes, brought to RT over 25 minutes, and partitioned between phosphate buffer (1 mol L^{-1}, pH 7, 20 mL) and Et_2O (20 mL). After extraction of the aqueous phase with Et_2O (2 × 20 mL) the combined organic phases were dried over Na_2SO_4 and the solvent removed in vacuum. Column chromatography on silica gel, eluting with pentane/Et_2O, gave the desired pure products.

Received: February 24, 2010
Published online: April 29, 2010

Keywords: cyclohexynes · fused-ring systems · medium-ring compounds · ring expansion · strained molecules

[1] Monographs on cycloalkynes: a) R. W. Hoffmann, *Dehydrobenzene and Cylcoalkynes*, Academic Press, New York, **1967**, pp. 317–357; b) R. Gleiter, R. Merger in *Modern Acetylene Chemistry* (Eds.: P. J. Stang, F. Diederich), VCH, Weinheim, **1995**, pp. 285–319; c) H. Hopf, *Classics in Hydrocarbon Chemistry*, Wiley-VCH, Weinheim, **2000**, pp. 156–160; for a review, see: A. Krebs, J. Wilke, *Top. Curr. Chem.* **1983**, *109*, 189–233.

[2] For theoretical studies on cyclohexyne, see: a) S. Olivella, M. A. Pericas, A. Riera, A. Sole, *J. Org. Chem.* **1987**, *52*, 4160–4163; b) R. P. Johnson, K. J. Daoust, *J. Am. Chem. Soc.* **1995**, *117*, 362–367; c) I. Yavari, F. Nasiri, H. Djahaniani, A. Jabbari, *Int. J. Quantum Chem.* **2006**, *106*, 697–703.

[3] Seminal publication: a) G. Wittig, *Naturwissenschaften* **1942**, *30*, 696–703; b) J. D. Roberts, H. E. Simmons, L. A. Carlsmith, C. W. Vaughan, *J. Am. Chem. Soc.* **1953**, *75*, 3290–3291; for recent applications in synthesis, see: c) R. L. Danheiser, A. L. Helgason, *J. Am. Chem. Soc.* **1994**, *116*, 9471–9479; d) U. K. Tambar, B. M. Stoltz, *J. Am. Chem. Soc.* **2005**, *127*, 5340–5341; for a recent review, see: e) R. Sanz, *Org. Prep. Proced. Int.* **2008**, *40*, 215–291.

[4] F. Scardiglia, J. D. Roberts, *Tetrahedron* **1957**, *1*, 343–344.

[5] a) P. Caubere, J. J. Brunet, *Tetrahedron* **1971**, *27*, 3515–3526; b) P. Caubere, J. J. Brunet, *Tetrahedron* **1972**, *28*, 4835–4845; c) P. Caubere, J. J. Brunet, *Tetrahedron* **1972**, *28*, 4847–4857; d) P. Caubere, J. J. Brunet, *Tetrahedron* **1972**, *28*, 4859–4869.

[6] The 6,6-*gem*-dimethyl substitution prevents competitive formation of the allene, see: B. Fixari, J. J. Brunet, P. Caubere, *Tetrahedron* **1976**, *32*, 927–934.

[7] For a review of [2+2] photocyclization/cyclobutene fragmentations in synthesis, see: W. Oppolzer, *Acc. Chem. Res.* **1982**, *15*, 135–141.

[8] For the calculation of ring strain, see: a) K. B. Wiberg, *Angew. Chem.* **1986**, *98*, 312–322; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 312–322; b) P. R. Khoury, J. D. Goddard, W. Tam, *Tetrahedron* **2004**, *60*, 8103–8112.

[9] a) L. Fitjer, U. Kliebisch, D. Wehle, S. Modaressi, *Tetrahedron Lett.* **1982**, *23*, 1661–1664; b) L. Fitjer, S. Modaressi, *Tetrahedron Lett.* **1983**, *24*, 5495–5498.

[10] For reviews on the influence of π-donor substituents on pericyclic reactions, see: a) N. D. Epiotis, *Angew. Chem.* **1974**, *86*, 825–855; *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 751–780; b) K. N. Houk, *Acc. Chem. Res.* **1975**, *8*, 361–369.

[11] D. A. Evans, A. M. Golob, *J. Am. Chem. Soc.* **1975**, *97*, 4765–4766.

[12] a) M. Fujita, Y. Sakanishi, W. H. Kim, T. Okuyama, *Chem. Lett.* **2002**, 908–909; 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*, 7548–7558; c) T. Okuyama, M. Fujita, *Acc. Chem. Res.* **2005**, *38*, 679–686.

[13] C. A. Brown, *J. Chem. Soc. Chem. Commun.* **1974**, 680–681.

[14] For further details, see the Supporting Information.

[15] Y. Mazur, F. Sondheimer, *J. Am. Chem. Soc.* **1958**, *80*, 5220–5229.

[16] A. D. Rodriguez, C. Ramirez, I. I. Rodriguez, *Tetrahedron Lett.* **1999**, *40*, 7627–7631.

[17] a) A. Eschenmoser, A. Frey, *Helv. Chim. Acta* **1952**, *35*, 1660–1666; b) C. A. Grob, W. Baumann, *Helv. Chim. Acta* **1955**, *38*, 594–610.

[18] We believe that the reaction proceeds through the enolate that is generated by H_2O-promoted desilylation under the basic reaction conditions.

[19] CCDC 767284 (**5 f**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[20] F. Allen, *Acta Crystallogr. Sect. B* **1984**, *40*, 64–72.

[21] Average values for *tert*-alcohols, as taken from: *CRC Handbook of Chemistry and Physics 89th ed.* (Ed.: D. R. Lide), CRC Press Taylor & Francis Group, Boca Raton, **2008**, pp. 9-1–9-16.

[22] a) N. G. Rondan, K. N. Houk, *J. Am. Chem. Soc.* **1985**, *107*, 2099–2111; b) B. K. Carpenter, *Tetrahedron* **1978**, *34*, 1877–1884.

[23] Only two X-ray crystal structures of cyclobutenols have been reported to date, and no correlation between structure and reactivity has been drawn, see: a) J. Suffert, B. Salem, P. Klotz, *J. Am. Chem. Soc.* **2001**, *123*, 12107–12108; b) B. Salem, J. Suffert, *Angew. Chem.* **2004**, *116*, 2886–2890; *Angew. Chem. Int. Ed.* **2004**, *43*, 2826–2830.