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BF_3-Catalyzed Skeletal Rearrangement of 7-En-2-ynones to *endo*-Type Cyclic Dienes

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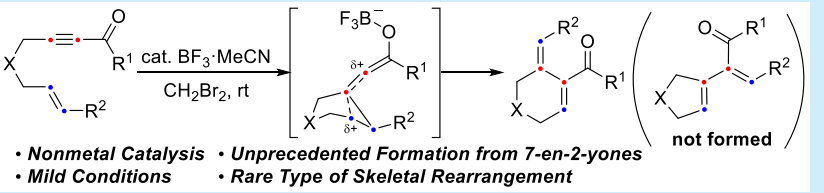
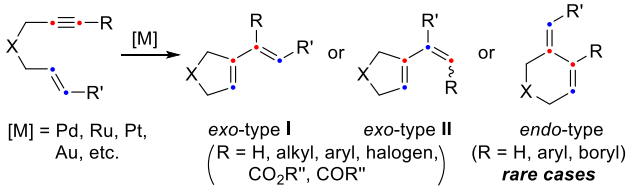


ABSTRACT: Transition-metal-catalyzed cycloisomerization reactions with skeletal rearrangement of 1,n-enynes to afford cyclic dienes (particularly *exo*-cyclization products) have been well studied. However, there are few reports on the nonmetal-catalyzed skeletal rearrangement of enynes and skeletal rearrangement of electron-deficient enynes such as n-en-2-ynones. Here, we describe BF_3·MeCN-catalyzed synthesis of 3-alkylidenecyclohexenes from 7-en-2-ynones, representing the first nonmetal-catalyzed skeletal rearrangement of 1,6-enynes to *endo*-type cyclic dienes.

Catalytic cycloisomerization reactions with skeletal rearrangement of 1,n-enynes afford diverse cyclic products, including cyclic conjugated dienes and bicyclic compounds, in a highly atom-economical manner.[1] In particular, skeletal rearrangement to form cyclic conjugated dienes, which can be regarded as a formal enyne metathesis, has great potential for application in the total synthesis of natural products and pharmaceuticals.[1f,g] Depending on the substitution pattern of substrates and the nature of the catalysts, 1,6-enynes can be converted into five-membered *exo*-type dienes **I** and **II** and six-membered *endo*-type dienes (Scheme 1). However, although

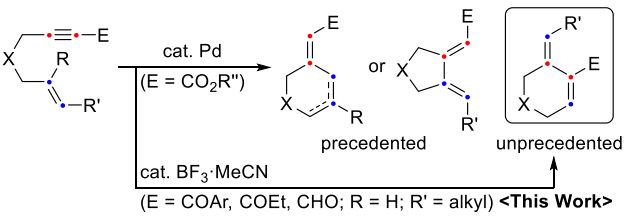
Scheme 1. Skeletal Rearrangements to Afford Cyclic Dienes



selective synthesis of *exo*-type **I**[2] and **II**[3] has been achieved by using various π-acidic metal complexes (Pd, Ru, Pt, Au, etc.), the exclusive formation of *endo*-type dienes has rarely been reported.[2e,4] Fürstner et al. have disclosed a selective synthesis of *exo*-type **I** by the skeletal rearrangement of an ynone-tethered cyclooctene using HBF_4 or BF_3·OEt_2.[5] Nevertheless, there has been no systematic study on nonmetal-catalyzed skeletal rearrangement of enynes.

As an extension of our research on metathesis-type reactions between alkynes and heteroenes catalyzed by σ-electrophilic acids,[6] we herein report catalytic skeletal rearrangement of 7-en-2-ynones into six-membered *endo*-type dienes using BF_3·MeCN as a σ-electrophilic nonmetallic catalyst (Scheme 2).

Scheme 2. Cycloisomerization of 7-En-2-ynoates or -ynones



Although Pd-catalyzed cycloisomerization without skeletal rearrangement of 7-en-2-ynoates into six-membered 1,3-dienes has been reported, six-membered 1,4-dienes or five-membered dienes (including the rearranged dienes in Scheme 1) are sometimes formed as byproducts (occasionally as the main products[2a−c,7]) (Scheme 2).[8] Therefore, the selective for-

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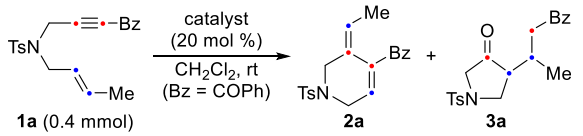
mation of six-membered 1,3-dienes from 7-en-2-ynones remains challenging.[9]

Initially, we focused on the evaluation of catalysts (20 mol %) for the cycloisomerization of 7-en-2-ynone **1a** in CH_2Cl_2 (Table 1). Our previous work on alkyne-carbonyl metathesis

Table 1. Evaluation of Catalysts



1a (0.4 mmol) **2a** **3a**

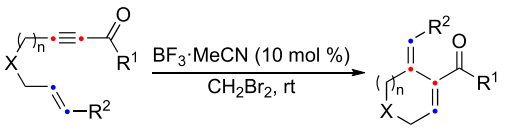
entry	catalyst	t (h)	**2a**[a] (%)	**3a**[a] (%)
1	IPy_2BF_4-2HBF_4[b]	8	38	23
2	NIS-HBF_4[b]	8	27	20
3	NIS-BF_3·OEt_2	24	46	17
4	NIS-BF_3·MeCN	5	48	10
5	BF_3·OEt_2	3	45	13
6	BF_3·MeCN	1	41	4
7	HBF_4[b]	1	37	20
8	TfOH	1	36	30
9	Tf_2NH	24	23	22
10	MsOH	24	0	0 (**1a**: 98)[c]
11	$B(C_6F_5)_3$	24	0	0 (**1a**: 73)[c]
12	$In(OTf)_3$	24	13[c]	13[c] (**1a**: 70)[c]
13	$Sc(OTf)_3$	24	0	0 (**1a**: 97)[c]
14	TMSOTf	24	43	17
15	$TrBF_4$	24	50	7
16[d]	BF_3·MeCN	4	60	5
17[d,e]	BF_3·MeCN	4	58	6

[a]Isolated yield. [b]Et_2O complex. [c]Determined by ^1H NMR. [d]BF_3·MeCN: 10 mol %, solvent: CH_2Br_2. [e]**1a**: 1 mmol.

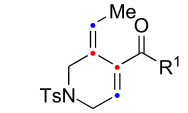
showed that IPy_2BF_4 (Py = pyridine) pretreated with HBF_4 (2 equiv to IPy_2BF_4) or a 1:1 mixture of *N*-iodosuccinimide (NIS) and acid was a more effective catalyst and exhibited a stronger σ-acidity than widely used nonmetal catalysts such as HBF_4 or BF_3·OEt_2.[6d] Therefore, these superelectrophilic iodine species were initially tested (entries 1−4). In contrast to Fürstner's report on the synthesis of *exo*-type dienes,[5] we obtained *endo*-type dienes **2a** in all cases in 27−48% yields at room temperature with no detectable formation of the corresponding *exo*-type dienes. Although cyclic ketone **3a** with cleavage of the triple bond was formed as a byproduct (10−23%) in these reactions, the NIS-BF_3·MeCN catalytic system led to the relatively selective formation of **2a** (**2a**:**3a** = 48:10, entry 4). To check the effect of NIS, we examined the sole use of BF_3 complexes, Brønsted acids, or other Lewis acids (entries 5−16). Even in the absence of NIS, BF_3·MeCN gave *endo*-type diene **2a** with high selectivity (**2a**:**3a** = 41:4, entry 6). On the other hand, when strong Brønsted acids such as HBF_4, TfOH, and Tf_2NH (Tf = CF_3SO_2) were employed, the yield of **2a** was reduced to 23−37%, concomitantly with an increased yield of cyclic ketone **3a** (20−30%, entries 7−9). Among the tested catalysts, $TrBF_4$ (Tr = trityl) resulted in the highest yield of **2a** (50%, entry 15); unfortunately, this could not be improved by changing the catalytic amount or solvent (see Supporting Information for details). However, by using 10 mol % of BF_3·MeCN in CH_2Br_2, which showed better results than many other solvents (see Supporting Information for details), the yield of **2a** was improved to 60% (entry 16). Furthermore, this catalytic system could be applied to the 1 mmol scale reaction (entry 17). It should be noted that the *endo*-type diene **2a** was obtained as a single stereoisomer (Table 1).[10]

With the optimal conditions in hand, we next investigated the scope of the present cycloisomerization, using various 7-en-2-ynones **1a**−**o** and 8-en-2-ynone **1p** (Scheme 3). Like phenyl

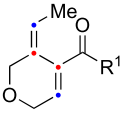
Scheme 3. Scope of Substrates[a]



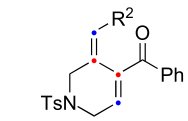
1a-o (n = 1), **1p** (n = 2) **2**



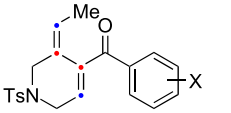
2a (R^1 = Ph) 60% (2 h)
2b (R^1 = Et) 79% (8 h)
2c (R^1 = H) 29% (1 h)[b]



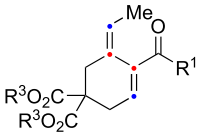
2j (R^1 = Ph) 50% (2 h)
2k (R^1 = Et) 61% (4 h)
2l (R^1 = Me) 46% (2 h)
2m (R^1 = H) 28% (1 h)[b,c]



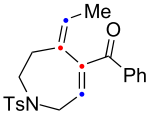
2q (R^2 = H) 18% (16 h)[e]
2r (R^2 = CH_2CH_2Ph) 44% (24 h)[g]



2d (X = 4-OMe) 43% (8 h)
2e (X = 4-Me) 59% (4 h)
2f (X = 4-Br) 68% (4 h)
2g (X = 4-NO_2) 51% (4 h)
2h (X = 3-Br) 62% (4 h)[b]
2i (X = 2-Br) 35% (4 h)[b]



2n (R^1 = Ph, R^3 = Me) 59% (24 h)[d]
2o (R^1 = Ph, R^3 = Et) 70% (24 h)
2p (R^1 = OMe, R^3 = Me) 0% (24 h)[d,e,f]



2s 55% (46 h)[h,i]

[a]Unless otherwise noted, only *E*-isomers of **1** were used. Reaction times are shown in parentheses. [b]BF_3·MeCN: 20 mol %. [c]*E*/:*Z* ratio of **1j** = 84:16. [d]*E*/*Z* ratio of **1k** or **1m** = 85:15. [e]BF_3·MeCN: 50 mol %. [f]Temp: 80 °C. [g]*E*/*Z* ratio of **1o** = 72:28. [h]*E*/*Z* ratio of **1p** = 80:20. [i]BF_3·MeCN: 30 mol %.

ynone **1a**, ethyl derivative **1b** and 4-substituted aryl derivatives **1d**−**g** were smoothly converted into the corresponding *endo*-type dienes **2b** and **2d**−**g** in 43−79% yield. In the case of 3- or 2-substituted aryl derivatives **1h**, **1i**, ynals **1c**, **1m**, and 8-en-2-ynone **1s**, increasing the amounts of BF_3·MeCN (20 or 30 mol %) afforded the *endo*-type dienes **2**, albeit in lower yield for **2c**, **2i**, and **2m** (28−35%). Furthermore, the optimal conditions were effective for the reaction of the ether-tethered **1j**−**m** and the malonate-tethered **1n** and **1o**. Unfortunately, the reaction of ynoate **1p** did not proceed even when 50 mol % of BF_3·MeCN was used at 80 °C for 24 h, and **1p** was recovered quantitatively. This may be due to the weaker electron-withdrawing ability of the alkoxy carbonyl group. Regarding substituents of alkenes, although the styrene derivative (R^1 = R^2 = Ph, X = O) easily underwent intramolecular Diels−Alder reaction,[11] unsubstituted **1q** and *E*-phenethyl-substituted **1r**, as well as *E*-Me-substituted **1a**−**o** and **1s**, all afforded *endo*-type dienes **2** with no detectable formation of the corresponding *exo*-type dienes.

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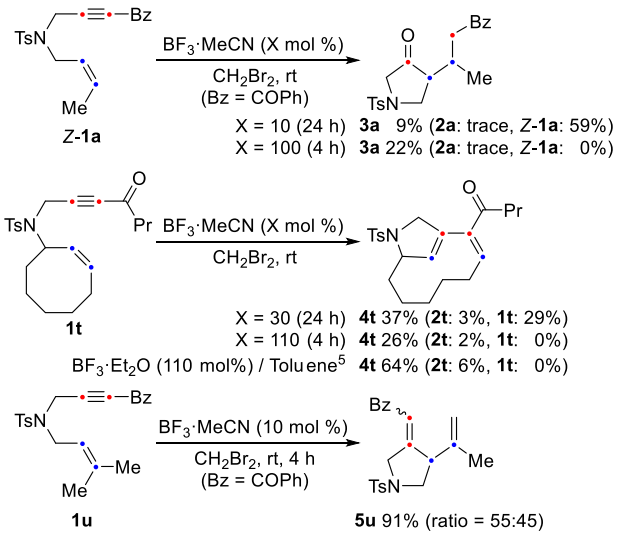
On the other hand, complete consumption of the *Z*-isomer of **1a** required 1 equiv of BF_3·MeCN, likely due to the low reactivity of *Z*-alkene for electrophilic addition, and cyclic ketone **3a** was obtained as a major product (Scheme 4).

Scheme 4. Reactions of *Z*-Disubstituted or Trisubstituted Alkenes



Regardless of the amount of BF_3·MeCN, cyclic alkene **1t** was also not converted into *endo*-type diene **2t**, but rather into *exo*-type diene **4t** as the major product. Fürstner et al. reported similar results using BF_3·Et_2O in toluene.[5] The trisubstituted **1u** preferentially underwent Alder-ene type reaction under the optimal conditions to give **5u** in 91% yield.

As mentioned above, ynone-tethered *E*-disubstituted alkenes were selectively converted into *endo*-type dienes by the present methods. To obtain mechanistic insight, DFT calculations were conducted using **1l** as a model substrate that reduces computational cost. The pathways for the peculiar skeletal rearrangements of **1l** catalyzed by BF_3 are summarized in Figure 1.

Initial interaction between **1l** and BF_3 generates an association complex **INT1** with a stabilization energy of 2.2 kcal/mol, which undergoes BF_3-mediated annulation (C2−C4 bond formation) *via* **TS1** to give **INT2** with an activation energy of 12.0 kcal/mol. As judged by the elongated C2−C3 bond distance (1.65 Å), as well as the near-linearity (168.9°) of the allene moiety, we consider **INT2** to be a zwitterionic intermediate in which the secondary carbocation at the C3 position is partially stabilized by the C1−C2 double bond. **INT2** is the bifurcating intermediate for the *endo*- and *exo*-type products. Notably, the delocalized cation species like **INT2** has been recognized as a reactive intermediate in various types of enyne cycloisomerization reactions.[5,12] For the *endo*-type product, the enolate anion (C1 carbon) in **INT2** attacks the C3 cation center, followed by BF_3-mediated C3−C4 bond cleavage/C2−C4 π bond formation, thereby giving rise to *endo*-type diene **INT3a** with a low activation energy (9.0 kcal/mol). Alternatively, **INT2** undergoes ring contraction (C−C bond rearrangement) to yield a five-membered ring transition state **TS2b**, and subsequently the enolate anion smoothly approaches the C4 carbocation along the intrinsic reaction coordinate to produce **INT3b** with a reasonably high stabilization energy (34.0 kcal/mol). **TS2a** is energetically

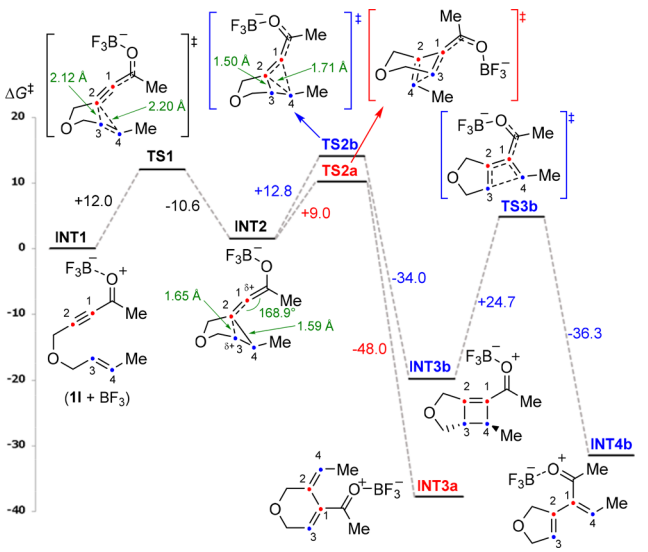
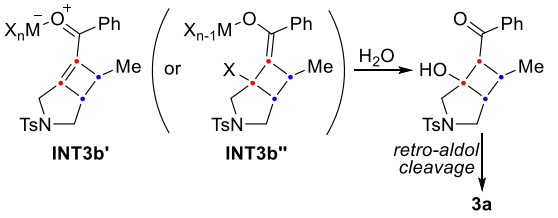


Figure 1. Gibbs free energy profile ($\Delta G^{\ddagger}$ in kcal/mol) of skeletal rearrangements of 7-en-2-ynone into cyclic dienes calculated by M06-2X/6-31+G(d).

more favorable than **TS2b** by 3.8 kcal/mol, since the ring contraction through C2−C4 bond scission causes a large energy loss. Thus, the production of the *endo*-type diene is favored kinetically and thermodynamically in this system. Concerning the *exo*-type product, since the activation energy of C3−C4 bond cleavage *via* **TS3b** to give **INT4b** is rather high ($\Delta G^{\ddagger}$ = 24.7 kcal/mol), **INT3b** would be more likely to undergo sequential hydration and retro-aldol cleavage reaction to give the **3a**-type product in some cases (Scheme 5).[13] In

Scheme 5. Proposed Mechanism for Formation of 3a



contrast, the corresponding intermediate derived from **1t** has a 3,4-cyclooctane-fused cyclobutene framework, whose C3−C4 bond is more easily cleaved than the case of unfused cyclobutene,[14] and thus would be transformed into *exo*-type diene **4t** (Scheme 4). On the other hand, the reaction pathways of the skeletal rearrangements of **1l** without an acid catalyst and with Brønsted acid, as shown in Figures S2−S4 (see Supporting Information), are similar to those with BF_3. However, (1) the activation energies without acid catalysts are much higher than those with BF_3 and (2) the activation energy difference at the bifurcating point with the Brønsted acid becomes very small. These calculated results are consistent with the experimental observations (Table 1).

In conclusion, we have developed a synthetic method for 3-alkylidenecyclohexenes by BF_3·MeCN-catalyzed skeletal rearrangement of 7-en-2-ynones. The present work is the first report of nonmetal-catalyzed skeletal rearrangement of 1,6-enyenes to afford *endo*-type cyclic dienes. Since the selective formation of six-membered 1,3-dienes from electron-deficient alkynes such as 7-en-2-ynoates is difficult by conventional

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methods,[2a−c,7,8] we believe that our findings not only open a new window on nonmetal-catalyzed skeletal rearrangements but also provide an attractive procedure for accessing six-membered 1,3-dienes.[15] Furthermore, based on DFT calculations and experimental data, we propose that the reaction proceeds via the bifurcating zwitterionic intermediate (**INT2**) in which the secondary carbocation at the C3 position is partially stabilized by the C1−C2 double bond. Studies on other skeletal rearrangements of n-en-2-ynones are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c00949.

Experimental procedures, compound characterization data, and computational details (PDF)

Accession Codes

CCDC 1975901 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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