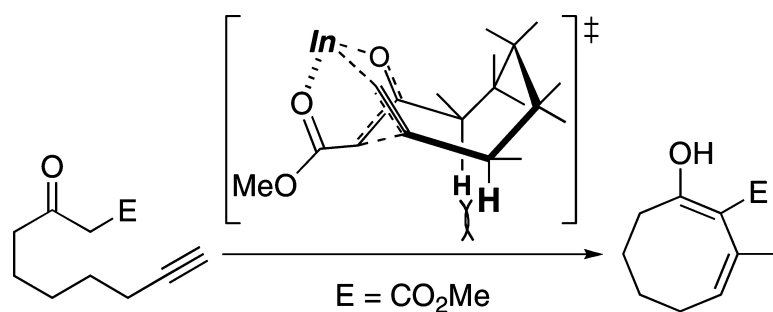Article

Efficient Formation of Ring Structures Utilizing Multisite Activation by Indium Catalysis

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Efficient Formation of Ring Structures Utilizing Multisite Activation by Indium Catalysis

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Abstract: Lewis acidic indium(III) salts, in particular $In(NTf_2)_3$, effect the conversion of α-(ω'-alkynyl)-β-ketoesters and ω-alkynyl-β-ketoesters to the corresponding cyclic products in a manner known as the Conia-ene reaction. This reaction can lead to the creation of five- to fifteen-membered-ring carbocycles and heterocycles in good to excellent yields. The synthetic features of the reaction are a relatively low catalyst loading, as low as 0.01 mol % in the best case, as well as no requirement of solvent for five-membered-ring formation and the requirement of only moderately dilute reaction conditions for medium-sized-ring formation. The high reactivity of indium salts is due to the double activation of the β-ketoester substrate containing an acetylene function. The indium metal activates the β-ketoester moiety by the formation of an indium enolate, and this indium metal electrophilically activates the alkyne moiety. Such a strong push−pull activation of the substrate by a single metal circumvents the disadvantage of entropic and enthalpic factors generally associated with the formation of medium- and large-sized rings. The reaction allows the ready formation of a fifteen-membered-ring carbocycle, from which *dl*-muscone has been synthesized.

Introduction

Conia-ene cyclization of an alkyne bearing an enolizable carbonyl group[1] is a classic example of a thermal ene reaction and has proved to be useful for the synthesis of five-membered rings. The utility of this cyclization methodology has been significantly expanded in recent years by the use of metal catalysts, which has allowed the reaction to proceed at lower temperatures and for a broader scope of substrates. A variety of Lewis acidic main-group and transition-metal atoms have been used in the recent examples.[2−13] In spite of such advances, the reaction has been a useful tool for five-membered-ring formation as in the original thermal Conia reaction, except for three cases[2−4] of six-membered rings. Advances toward formation of larger rings were reported in 2007. Sawamura and co-

workers[13] reported that gold catalysis enables the formation of a seven-membered ring, and we reported that indium is useful for the formation of a variety of seven- to fifteen-membered-ring carbocyclic and heterocyclic compounds.[14,15] This article fully describes this indium-mediated Conia-ene-type reaction.

Four types of mechanisms have been suggested for the reported metal-mediated Conia cyclization leading to five- to seven-membered rings (Figure 1): (a) addition of a metal enolate to the internal alkyne,[3,4] (b) addition of an enol to a metal/alkyne π complex,[9,11] (c) ene−yne activation,[5,6,12] and (d) activation of the enol moiety and the alkyne by two different metal atoms.[8,10] A few years ago we discovered that indium(III) tris(trifluoromethanesulfonate), $In(OTf)_3$, is an extremely efficient catalyst for the intermolecular addition of a β-ketoester to an unactivated alkyne.[16] Theoretical calculations suggested that this addition reaction involves a defined double-activation mechanism where the indium metal electrophilically activates the alkyne to which the ene part of the indium enolate adds nucleophilically (Figure 2).[16d] We considered that this mechanism for the $In(OTf)_3$-catalyzed reaction as applied to medium-

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(1) Conia, J. M.; Le Perchec, P. *Synthesis* **1975**, 1–19.

(2) For Zn-mediated reactions, see: Nakamura, E.; Sakata, G.; Kubota, K. *Tetrahedron Lett.* **1998**, *39*, 2157–2158.

(3) For Ti-mediated reactions, see: Kitagawa, O.; Suzuki, T.; Inoue, T.; Watanabe, Y.; Taguchi, T. *J. Org. Chem.* **1998**, *63*, 9470–9475.

(4) For Sn-mediated reactions, see: Kitagawa, O.; Fujiwara, H.; Suzuki, T.; Taguchi, T.; Shiro, M. *J. Org. Chem.* **2000**, *65*, 6819–6825.

(5) For Ni catalysis, see: Gao, Q.; Zheng, B.-F.; Li, J.-H.; Yang, D. *Org. Lett.* **2005**, *7*, 2185–2188.

(6) For Co catalysis, see: Cruciani, P.; Stammler, R.; Aubert, C.; Malacria, M. *J. Org. Chem.* **1996**, *61*, 2699–2708.

(7) For Mo catalysis, see: McDonald, F. E.; Olson, T. C. *Tetrahedron Lett.* **1997**, *38*, 7691–7692.

(8) For Cu catalysis, see: (a) Bouyssi, D.; Monteiro, N.; Balme, G. *Tetrahedron Lett.* **1999**, *40*, 1297–1300. (b) Deng, C.-L.; Song, R.-J.; Guo, S.-M.; Wang, Z.-Q.; Li, J.-H. *Org. Lett.* **2007**, *9*, 5111–5114.

(9) For Pd catalysis, see: Lomberget, T.; Bouyssi, D.; Balme, G. *Synthesis* **2005**, 311–329.

(10) For enantioselective Pd catalysis, see: Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 17168–17169.

(11) For Au catalysis, see: (a) Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 4526–4527. (b) Staben, S. T.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 5350–5352. (c) Pan, J.-H.; Yang, M.; Gao, Q.; Zhu, N.-Y.; Yang, D. *Synthesis* **2007**, 2539–2544.

(12) For Re catalysis, see: Kuninobu, Y.; Kawata, A.; Takai, K. *Org. Lett.* **2005**, *7*, 4823–4825.

(13) Ochida, A.; Ito, H.; Sawamura, M. *J. Am. Chem. Soc.* **2006**, *128*, 16486–16487.

(14) Tsuji, H.; Yamagata, K.-i.; Itoh, Y.; Endo, K.; Nakamura, M.; Nakamura, E. *Angew. Chem., Int. Ed.* **2007**, *46*, 8060–8062.

(15) Hatakeyama and co-workers recently reported on the formation of five- to seven-membered heterocyclic ring systems using $In(OTf)_3$ catalysis: Takahashi, K.; Midori, M.; Kawano, K.; Ishihara, J.; Hatakeyama, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 6244–6246.

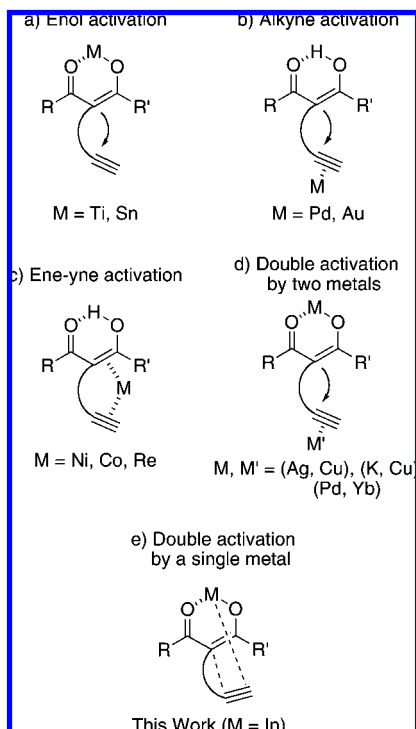**Figure 1.** Proposed activation mechanisms in metal-mediated Conia-ene cyclization.

Figure 2. Schematic illustration of the calculated transition state for intermolecular In(OTf)$_3$-catalyzed addition of a 1,3-dicarbonyl compound to acetylene.

sized-ring synthesis (Figure 1e) would overcome the entropic and enthalpic problems associated with the formation of medium-sized rings: a higher entropy barrier than for the formation of three- to six-membered rings and an unfavorable enthalpy barrier because of transannular interactions in the formation of rings containing more than seven members. Medium-sized rings are found in a number of biologically active natural products,[17,18] and their synthesis has long been a challenge for synthetic chemists.[19,20]

Results and Discussion

Cyclization of α-(ω'-Alkynyl)-β-ketoesters. The mode of cyclization in most of the reported thermal and metal-mediated Conia-ene reactions, i.e., cyclization of α-(ω'-alkynyl)-β-ketoesters (mode A), is shown in eq 1; however, an alternative cyclization mode using ω-alkynyl-β-ketoesters (mode B),[8b,13] as shown in eq 2, appeared to us to be equally feasible. Both modes A and B were examined in this study. First, we describe the results of the conventional cyclization via mode A and its use in the synthesis of five- to seven-membered rings. Second, we describe the use of mode B for the formation of six- to fifteen-membered rings.
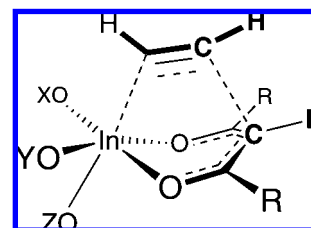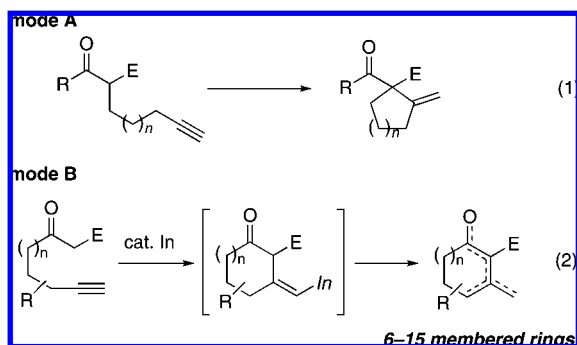
First, we examined mode A and its efficacy for the formation of five- to six-membered rings. We found that the reaction takes place cleanly without solvent and at low catalyst loading [0.01 mol % of In(OTf)$_3$] for five-membered-ring formation. The substrate **1s** gave the desired methylenecyclopentane compound **1a** in 99% isolated yield (Table 1, entry 1) after 24 h with stirring at 60 °C. An acid-sensitive allyl ester **2s** and an aroyl substrate **3s** gave **2a** and **3a** in 93 and 78% yields, respectively (entries 2 and 3). The use of a larger amount of the catalyst resulted in the isomerization of the *exo*-methylene double bond in the initial product to an internal position (data not shown). The cyclization of iodoalkynyl compound **3s'** proceeded in toluene at 40 °C to give the expected alkenyl iodide product **3a'** having exclusively *E* geometry in 91% yield (entry 4). This stereoselectivity suggests that the addition of an indium enolate intermediate to the C≡C triple bond occurs in a cis fashion, as previously reported for the intermolecular valiant of the reaction (see Figure 2).[16] Six-membered-ring formation was completed in 12 h in the presence of 1 mol % In(OTf)$_3$ at 80 °C in toluene (0.5 M) to give the six-membered-ring product **4a** in 95% isolated yield (entry 5). The use of In(NTf$_2$)$_3$ accelerates the reaction to complete in 4 h to afford **4a** in 98% isolated yield (entry 6).

Seven-membered-ring formation proceeded slowly. The reaction of **5s** in the presence of 1 mol % In(OTf)$_3$ gave the product **5a** in 40% yield (Table 2, entry 1) after 1 h at 150 °C in 0.1 M toluene. Changing the counteranion (Cl, OTf, ONf,[21] and

(16) (a) Nakamura, M.; Endo, K.; Nakamura, E. *J. Am. Chem. Soc.* **2003**, *125*, 13002–13003. (b) Nakamura, M.; Endo, K.; Nakamura, E. *Org. Lett.* **2005**, *7*, 3279–3281. (c) Nakamura, M.; Endo, K.; Nakamura, E. *Adv. Synth. Catal.* **2005**, *347*, 1681–1686. (d) Endo, K.; Hatakeyama, T.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2007**, *129*, 5264–5271. (e) Tsuji, H.; Fujimoto, T.; Endo, K.; Nakamura, M.; Nakamura, E. *Org. Lett.* **2008**, *10*, 1219–1221. (f) Fujimoto, T.; Endo, K.; Tsuji, H.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 4492–4496.

(17) For recent examples, see: (a) Fraga, B. M. *Nat. Prod. Rep.* **2003**, *20*, 392–413. (b) Faulkner, D. J. *Nat. Prod. Rep.* **1999**, *16*, 155–198.

(18) For selected recent reviews, see: (a) Booker-Milburn, K. I.; Sharpe, A. *J. Chem. Soc., Perkin Trans 1* **1998**, 983–1006. (b) Molander, G. *Acc. Chem. Res.* **1998**, *31*, 603–609. (c) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881–930. (d) Yet, L. *Chem. Rev.* **2000**, *100*, 2963–3007.

(19) For reviews, see: (a) Winnik, M. A. *Chem. Rev.* **1981**, *81*, 491–524. (b) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95–102. (c) Galli, C.; Mandolini, L. *Eur. J. Org. Chem.* **2000**, 3117–3125.

(20) One of the most famous medium-sized-ring formation reactions is ring-closing metathesis. For recent reviews, see: (a) Maier, M. E. *Angew. Chem., Int. Ed.* **2000**, *39*, 2073–2077. (b) Michaut, A.; Rodriguez, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 5740–5750. For examples, see: (c) Schrock, R. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 3748–3759. (d) Grubbs, R. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 3760–3765.

(21) ONf (nonaflate) = OSO$_2$C$_4$F$_9$; see: Tsuchimoto, T.; Matsubayashi, H.; Kaneko, M.; Shirakawa, E.; Kawakami, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 1336–1340.

Table 1. Formation of Five- and Six-Membered Rings Using Indium Salts (Mode A)
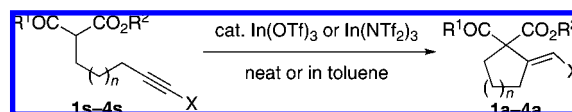
entry	substrate	conditions	product[a]	yield[b]
1	**1s** ($n = 1$, X = H, R^1 = Me, R^2 = Et)	In(OTf)$_3$, 0.01 mol %, neat, 60 °C, 24 h	**1a** (5)	99%
2	**2s** ($n = 1$, X = H, R^1 = Me, R^2 = allyl)	In(OTf)$_3$, 0.01 mol %, neat, 60 °C, 36 h	**2a** (5)	93%
3	**3s** ($n = 1$, X = H, R^1 = Ph, R^2 = Et)	In(OTf)$_3$, 0.01 mol %, neat, 60 °C, 72 h	**3a** (5)	78%
4	**3s′** ($n = 1$, X = I, R^1 = Ph, R^2 = Et)	In(NTf$_2$)$_3$, 1 mol %, 0.5 M, 40 °C, 16 h	**3a′** (5)	91%
5	**4s** ($n = 2$, X = H, R^1 = Me, R^2 = Me)	In(OTf)$_3$, 1 mol %, 0.5 M, 80 °C, 12 h	**4a** (6)	95%
6	**4s** ($n = 2$, X = H, R^1 = Me, R^2 = Me)	In(NTf$_2$)$_3$, 1 mol %, 0.5 M, 80 °C, 4 h	**4a** (6)	98%

[a] The number in parentheses is the number of members in the product ring. [b] Isolated yield.

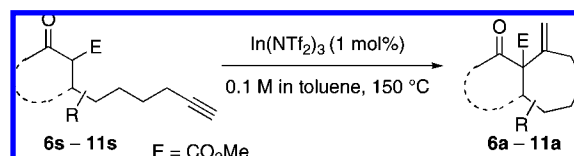**Table 2.** Seven-Membered-Ring Formation and Catalyst Screening
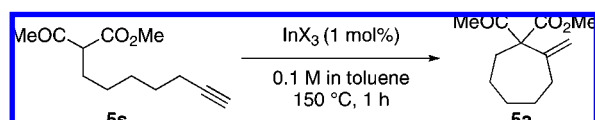
entry	X	yield[a]
1	OTf	40%
2	ONf	67%
3	NTf$_2$	75%
4	NTf$_2$	93%[b]
5	Cl	0%

[a] NMR yield determined using bromoform as an internal standard. [b] Isolated yield after 2 h.

NTf$_2$[22]) revealed that NTf$_2$ is the best catalyst for this reaction, giving a 93% yield after 2 h of reaction time (entry 4). Steric bulkiness of the NTf$_2$ group, which could prevent the deactivation of the indium metal by extra coordination, could account for the high reactivity.[23]

In(NTf$_2$)$_3$ was found to be the catalyst of choice for seven-membered-ring cyclization reactions (Table 3). We first focused on bicyclo[5.3.0]decanes in view of the ubiquity of such rings among sesquiterpenes. The cyclization of 2-methoxycarbonyl-3-(hept-6-yl)cyclopentanone **6s**, which was used as a diastereomeric mixture, afforded the cis-fused cyclization product **6a** as a single diastereomer in 81% yield (entry 1). The reaction was slightly slower than that of the parent substrate **5s**, reaching completion after 14 h at 150 °C. Similarly, the corresponding cyclohexanone **7s** produced bicyclo[5.4.0]undecanone **7a** in 84% yield with high diastereoselectivity, namely, a 93:7 mixture of cis and trans isomers (entry 2). The cis junction in these products was determined by nuclear Overhauser effect (NOE) analysis of their derivatives (see the Supporting Information). Cyclization of an enyne substrate **8s** afforded an intriguing cycloheptane **8a** containing a conjugated diene structure in 91% yield (entry 3). The example in entry 4 illustrates the synthesis of a nitrogen-containing seven-membered ring **9a** (83% yield) from compound **9s**, where the nitrogen atom is protected by a readily removable 2-nitrobenzenesulfonyl (Ns) group.[24] Substrates bearing a substituent at the β position (R = Et in **10s** and R = Ph in **11s**) gave **10a** and **11a** in 85 and 94% yields with 93:7 and 96:4 diastereomeric ratios, respectively (entries 5 and 6).

(22) Frost, C. G.; Hartley, J. P.; Griffin, D. *Tetrahedron Lett.* **2002**, *43*, 4789–4791.
(23) No reaction took place in a coordinative solvent such as tetrahydrofuran or dimethylformamide.
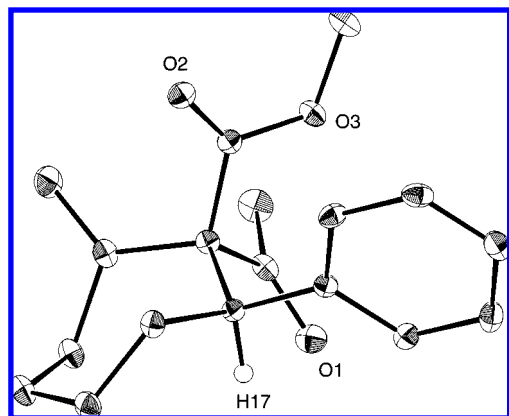(24) Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353–359.

Table 3. Seven-Membered-Ring Formation

entry	substrate	reaction time	product[a]	total yield[b]
1	**6s**	14 h	**6a**	81%
2	**7s**	108 h	**7a** (93:7)	84%
3	**8s**	24 h	**8a**	91%
4	**9s**	48 h	**9a**	83%
5	**10s** (R = Et)	36 h	**10a** (93:7)	85%
6	**11s** (R = Ph)	1 h	**11a** (96:4)	94%

[a] The major diastereomer is shown. The ratio in parentheses refers to the diastereomeric ratio. [b] Isolated yield.

The stereochemistry of the major diastereomer **11a** was determined by X-ray crystallography to have the R group positioned cis to the ester group (Figure 3). The diastereoselectivity could be rationalized in terms of steric repulsion between the R group and the methyl ketone, assuming that the two hydrogen atoms occupy two diaxial positions (Figure 4). Interestingly, the phenyl compound was as reactive (1 h, 150 °C) as the nonsubstituted compound **5s**, while the ethyl compound was much less reactive (36 h at 150 °C). This is probably a result of the steric hindrance between the R group and the ester moiety (see Figure 4, major pathway). Because of

Figure 3. ORTEP drawing of the seven-membered-ring product **11a** (50% probability for thermal ellipsoids). Hydrogen atoms, except for H17, have been omitted for clarity.
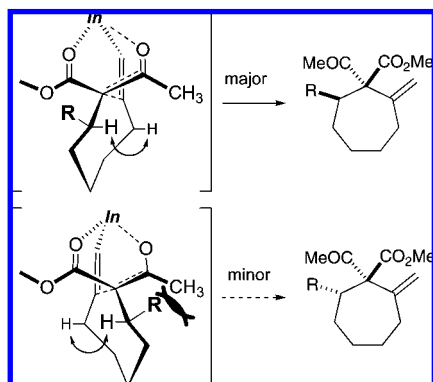

Figure 4. Possible pathways leading to the major and minor diastereomers in the cyclizations of **10s** and **11s**.

its flatness, the Ph group could avoid steric repulsion with the ester group by rotational motion, while the Et group could not since all of the carbon atoms are sp³-hybridized.

Cyclization of ω-Alkynyl-β-ketoesters. Despite the excellent performance of In(NTf₂)₃ in the conversion of α-(ω′-alkynyl)-β-ketoesters into five- to seven-membered rings, we could not readily form an eight-membered ring by means of the mode A cyclization (eq 3). We considered that transannular steric interaction starts to interfere with the cyclization of an eight-membered ring.
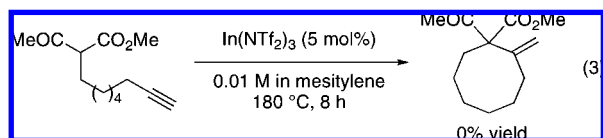
Cyclooctane[25] is known to have several hydrogen atoms pointing toward the inside of the ring, causing energetically unfavorable transannular steric interactions (Figure 5). Replacement of two sp³ carbon atoms (at the 1 and 3 positions, for instance) by sp² carbon atoms can reduce the ring strain.

Thus, we considered a strategy of cyclization that includes sp² carbon atoms in the ring structure involved in the transition state for medium-sized-ring formation (Figure 6a,b). To this end, we examined the reaction of ω-alkynyl-β-ketoesters. As exem-
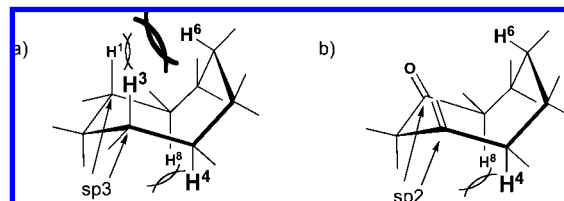
(25) For stable conformations of medium-sized cycloalkanes, see: Dale, J. *Topics Stereochem.* **1976**, *9*, 199–270.

Figure 5. Schematic representations of eight-membered rings: (a) cyclooctane; (b) 3-methylenecyclooctanone.
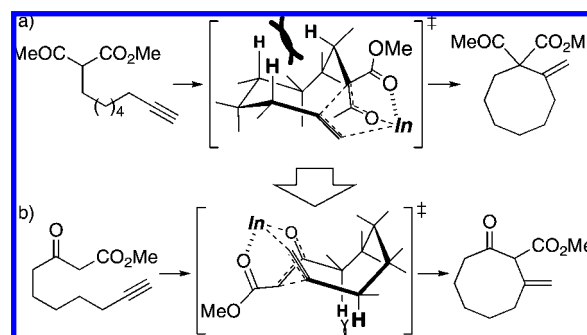

Figure 6. Schematic representations of transition states for eight-membered-ring formation: (a) α- to α-cyclization (mode A); (b) γ- to α-cyclization (mode B).

plified by a comparison of panels a and b of Figure 6, the latter reactant will suffer less from the transannular steric interactions.[26]

This idea was first tested on the formation of six- and seven-membered rings (Table 4).[27] The expected six-membered ring **12b** was obtained from **12s** in 90% yield exclusively in its enone form (entry 1). Seven-membered-ring formation took place much faster and in better yield than six-membered-ring formation under the same reaction conditions (entry 2). In the seven-membered-ring formation reaction, the catalyst loading could be reduced to 0.1 mol % and a good yield could still be obtained (entry 3). The seven-membered ring was obtained as a mixture of the double-bond isomers **13b** and **13c**, most likely because of isomerization of the initial product **13a** to **13b** and then to **13c**.

When the reaction was carried out using the substrate **14s**, the eight-membered-ring product **14c** was obtained in 51% yield (Table 5, entry 1). The structure was unambiguously determined by single-crystal X-ray structure analysis (Figure 7). The product was obtained as a double-bond isomer of the expected product **14a**. The X-ray structure (Figure 7) shows that the transannular steric interaction is effectively reduced as compared with that in all-sp³-carbon cyclooctane (Figure 5). It is noteworthy that the cyclization reaction took place in high yield in a 0.1 M solution of toluene, a concentration considered unusually high for medium-sized-ring formation.

Incorporation of an additional sp² carbon center in the ring system gave the corresponding eight-membered ring in even higher yield. A substrate bearing a phenylacetylene moiety (**15s**) gave the product in 75% yield (Table 5, entry 2). The substrate **16s** is a more sp²-enriched compound and gave a dibenzocyclooctane structure in 89% yield (entry 3). The product **16a**

(26) After our communication (ref 14), Li et al. (ref 8b) reported on a similar strategy.

(27) The five-membered-ring formation gave a furan derivative because of an oxygen-centered cyclization rather than the expected carbon-centered cyclization.

Table 4. Six- and Seven-Membered-Ring Formation Reaction Using ω-Alkynyl-β-ketoesters (Mode B)
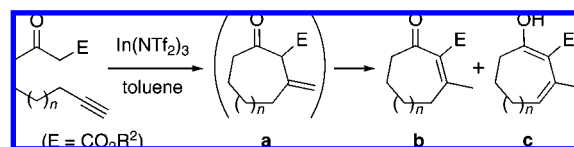
entry[a]	substrate	conditions	product[b]	total yield[c]
1	**12s** ($n = 0$, $R^2 = $ Et)	1 mol %, 0.1 M, 100 °C, 10 h	**12b** (6)	90%
2	**13s** ($n = 1$, $R^2 = $ Me)	1 mol %, 0.1 M, 100 °C, 2 h	**13b** + **13c** (7) (38 : 62)	98%
3	**13s** ($n = 1$, $R^2 = $ Me)	0.1 mol %, 0.1 M, 120 °C, 12 h	**13b** + **13c** (7) (60 : 40)	81%

[a] The initial cyclization product **a** isomerized in situ to **b** and/or **c** and hence could not be isolated. [b] The number in parentheses is the number of members in the product ring. [c] Isolated yield.

Table 5. Eight-Membered-Ring Formation (Mode B)
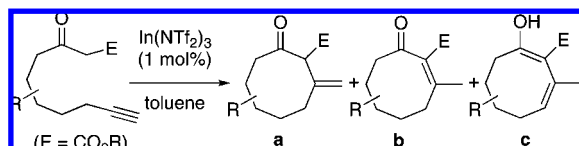
entry	substrate	conditions	product	yield[a]
1	**14s** (R = Me)	0.1M 120 °C, 12 h	**14c**	51%
2	**15s** (R = Et)	0.1 M 100 °C, 2 h	**15a**[b] + **15b** (23 : 77)	75%
3	**16s** (R = Et)	0.05 M 100 °C, 1 h	**16a**[c]	89%

[a] Isolated yield. [b] Keto form 100%. [c] Keto/enol = 47/53; keto major/minor = 90/10; enol major/minor = 94/6.

was obtained as a mixture of enol and keto tautomers, and the latter involved diastereomers in a ratio of 90:10 because of the existence of one central chirality at the α-position of the ester moiety and another axial chirality of the biphenyl moiety. A dibenzocyclooctane derivative is a core architecture in some biologically active natural products, such as lignans.[28]

Formation of nine- and ten-membered rings was more difficult. Cyclononane suffers greater transannular steric repulsion, and thus, the simple substrate **17s** gave the nine-membered-ring product in only 7% yield (Table 6, entry 1). Substrates incorporating sp^2 carbon atoms or an sp^3 nitrogen atom were effective, even for 9- and 10-membered-ring formation. Thus,

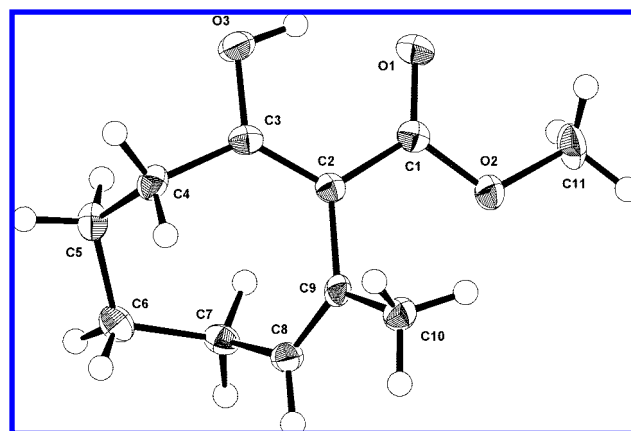(28) For a recent review, see: Chang, J.; Reiner, J.; Xie, J. *Chem. Rev.* **2005**, *105*, 4581–4609.

Figure 7. ORTEP drawing of the eight-membered-ring product **14c** (50% probability for thermal ellipsoids). Selected bond lengths (Å): C(2)−C(3), 1.3596(19); C(2)−C(9), 1.4866(19); C(8)−C(9), 1.3358(19); C(9)−C(10), 1.5113(19).
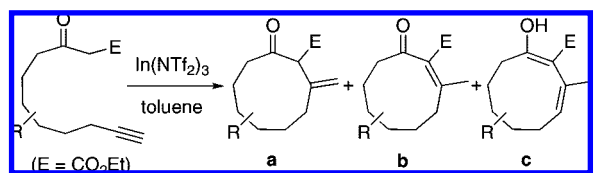
a ketoester with a phenylene moiety, **18s**, afforded benzo-fused nine-membered-ring products **18a** and **18b** in 71% yield as a mixture of double-bond isomers (entry 2).[29] A substrate **19s** with an *N-p*-toluenesulfonyl (Ts) group afforded nine-membered-ring heterocycles **19a** and **19b** in 61% yield (entry 3). The optimum reaction conditions required 10 mol % of the In(NTf$_2$)$_3$ catalyst in order to avoid competitive loss of the ethoxycarbonyl group, which became predominant in the reaction with a low catalyst loading (i.e., slow cyclization). Similarly, substrate **20s** gave the expected ten-membered-ring product **20a** in 74% yield exclusively in its enol form and as a single diastereomer (eq 4). The stereochemistry of the crystalline dibenzocyclodecane **20a** was determined by single-crystal X-ray structural analysis (Figure 8).
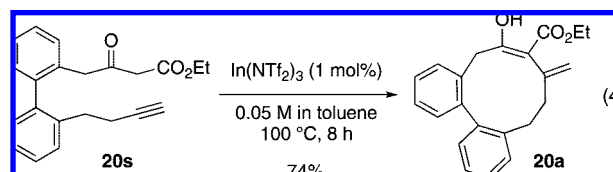
The indium-catalyzed cyclization methodology was found to be applicable to the formation of a larger ring as well. Formation

(29) The cyclization of **18s** did not proceed at all with AuCl(PPh$_3$) (1 mol %) and AgOTf (1 mol %) at room temperature in CH$_2$Cl$_2$ (0.4 M) over 48 h, which was effective for five-membered-ring formation in ref 11a. Even when the same reaction conditions as for In(NTf$_2$)$_3$ (0.05 M in toluene, 120 °C, 24 h) were used, the Au catalyst system could not make the reaction proceed.

Table 6. Nine-Membered-Ring Formation

entry	substrate	conditions	product	yield[a]
1	**17s**	1 mol%, 0.04 M 150 °C, 8 h	**17c**	7%
2	**18s**	1 mol%, 0.05 M 120 °C, 12 h	**18a**[b] + **18b** (15 : 85)	71%
3	**19s**	10 mol%, 0.04 M 150 °C, 1.5 h	**19a**[c] + **19b** (85 : 15)	61%

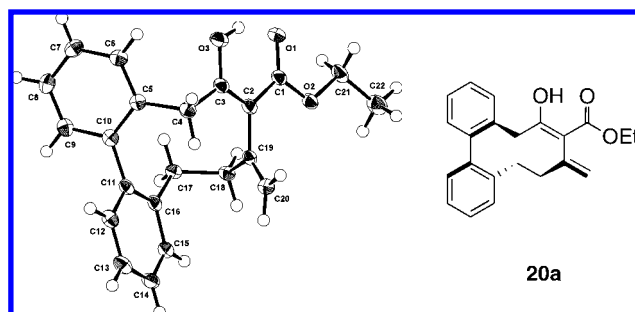[a] Isolated yield. [b] Keto/enol = 11/89. [c] Keto/enol = 34/66.

Figure 8. ORTEP drawing of the ten-membered-ring product **20a** (50% probability for thermal ellipsoids). Selected bond lengths (Å): C(1)−C(2), 1.4626(17); C(2)−C(3), 1.3587(18); C(2)−C(19), 1.4959(15); C(19)−C(20), 1.3208(18).

of a fifteen-membered ring from **21s** took place in a 0.01 M toluene solution to give the product **21a** in 27% yield (Scheme 1). The product **21a** was transformed into (±)-muscone by hydrogenation followed by decarboxylation.[30]

Conclusions

In this article, we have reported on an effective construction of five- to fifteen-membered rings by Conia-ene-type cyclization of α-(ω′-alkynyl)-β-ketoesters and ω-alkynyl-β-ketoesters. The first key issue is the use of indium(III) catalysts, in particular In(NTf$_2$)$_3$, which enable push−pull double activation of the acetylenic triple bond, strongly organize the transition state of the cyclization by means of multisite interactions, and allow

Scheme 1
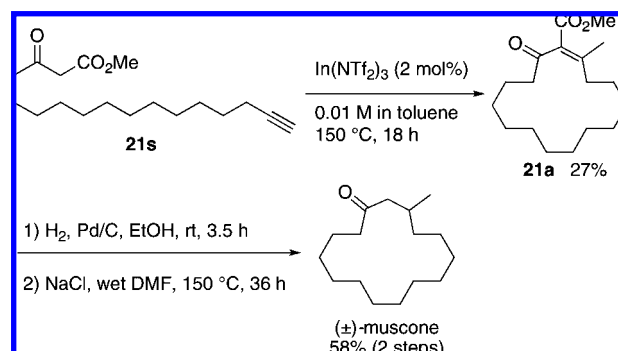
the system to overcome the entropy and enthalpy barriers inherent in the formation of medium- to large-sized rings. The second key issue is the study of the substrate structure. The large difference between α-(ω′-alkynyl)-β-ketoesters and ω-alkynyl-β-ketoesters with respect to the ease of cyclization to form the ring systems is quite remarkable.[31] The former substrates are the best for the five-membered rings, while the latter are the best for the seven-membered rings, as studied for simple methylene-tethered substrates. Of even greater interest is the difference in the formation of eight-membered rings. The former failed almost entirely, while the latter cyclized very well. With careful design of substrates to reduce transannular steric interactions, the latter type of substrate readily gave medium- to large-sized rings. The overall features of the present cyclization strategy include the relatively low catalyst loading, as low as 0.01 mol % in the best case, as well as the requirement of no solvent for five-membered-ring formation and only moderately dilute reaction conditions for medium-sized-ring formation. As a result of the present demonstration of the high synthetic potentials of indium(III) enolate chemistry, we expect that further investigations into the use of indium metals in organic chemistry will be worthwhile.

Experimental Section

Typical Experimental Procedure for In(OTf)$_3$-Catalyzed Cycloisomerization (Mode A): Ethyl 1-(1-Oxoethyl)-2-methylenecyclopentanecarboxylate (1a). A solution of In(OTf)$_3$ in THF (0.036 M, 2.75 mL, 0.10 μmol) was added to a dry vessel under an argon atmosphere, and THF was removed in vacuo at 60 °C. Substrate **1s** (194.5 mg, 1.0 mmol) was added to the reaction vessel, and the mixture was stirred at 60 °C for 24 h. The reaction mixture was diluted with hexane and then filtered through a pad of Celite and washed with hexane. The filtrate was concentrated in vacuo to obtain an oily crude product. Flash column chromatography on silica gel (eluent: 90/10 hexane/ethyl acetate) yielded the title compound **1a** (192.1 mg, 99%) as a colorless oil. NMR spectra were in good accordance with those in the literature.[32]

Typical Experimental Procedure for In(NTf$_2$)$_3$-Catalyzed Cycloisomerization (Mode A): Methyl 1-(1-Oxoethyl)-2-methylenecycloheptanecarboxylate (5a). A dry reaction vessel was charged with a solution of In(NTf$_2$)$_3$ in acetonitrile (0.05 M, 60 μL, 3.0 μmol). Acetonitrile was removed under vacuum (0.5 Torr) at 60 °C for 1 h. After the reaction vessel was cooled to room temperature, toluene (3 mL) and substrate **5s** (63 mg, 0.30 mmol) were added successively. The mixture was heated at 150 °C for

(30) Tanabe, Y.; Matsumoto, N.; Higashi, T.; Misaki, T.; Itoh, T.; Yamamoto, M.; Mitarai, K.; Nishii, Y. *Tetrahedron* **2002**, *58*, 8269–8280, and references cited therein.

(31) Hatakeyama and co-workers (ref 15) reported the use of malonates and internal alkynes as reactive substrates for In(OTf)$_3$-catalyzed Conia-ene-type cyclization.

(32) Boaventura, M. A.; Drouin, J.; Conia, J. M. *Synthesis* **1983**, 801–804.

2 h. The resulting mixture was cooled to room temperature and then filtered through a thin pad of silica gel with elution of ether. The organic solvent was removed in vacuo to yield the crude product. Flash column chromatography on silica gel (eluent: 90/10 hexane/ether) yielded the title compound as a colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$): δ 1.25−1.56 (m, 4H), 1.68−1.80 (m, 3H), 2.00−2.06 (m, 2H), 2.22 (s, 3H), 2.39−2.43 (m, 1H), 3.76 (s, 3H), 4.93 (s, 1H), 5.25 (s, 1H). ^{13}C NMR (125 MHz, CDCl$_3$): δ 24.8, 27.1, 30.5, 30.8, 33.0, 35.6, 52.3, 69.7, 117.8, 147.1, 172.8, 204.5. FTIR (cm^{-1}): 2928, 2858, 1744, 1710, 1630, 1446, 1434, 1355, 1233, 1202, 1183, 1140, 1050, 903. Anal. Calcd for C$_{12}$H$_{19}$O$_3$: C, 68.54; H, 8.63. Found: C, 68.45; H, 8.87.

Supporting Information Available: Experimental details and CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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