Medium-Sized Rings

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Indium-Catalyzed Cycloisomerization of ω-Alkynyl-β-ketoesters into Six- to Fifteen-Membered Rings**

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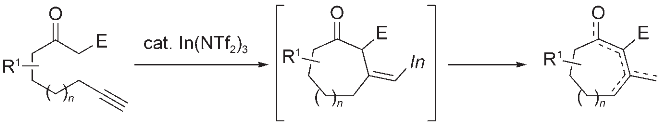
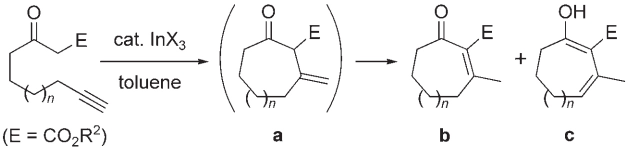
The ene reaction between an enol and an alkyne is an established synthetic reaction with respect to its five-membered-ring-forming variant, known as the Conia reaction.[1,2] Recent reports on transition-metal catalysis have described several examples of the extension of the reaction to six- and seven-membered carbocycles,[2a,f,i,3] yet it is entirely unknown whether or not the reaction is applicable to the synthesis of larger rings. Herein, we report that an indium salt catalyzes the cycloisomerization of ω-alkynyl-β-ketoesters to provide an effective synthetic method of medium- to large-sized rings (Scheme 1) based on a dual activation mechanism. Unusual and synthetically valuable features of the present reaction are that it allows the formation of seven-to-fifteen-membered rings under moderately dilute conditions and that some medium-sized rings form readily, even more readily than a six-membered ring. The reaction provided access to (±)-muscone[4] as well as ring systems related to lignans.[5]



Scheme 1. Indium-catalyzed cycloisomerization of ω-alkynyl-β-ketoesters. Tf = trifluoromethanesulfonyl.

Medium-sized rings frequently appear in the structures of natural products.[6] Their formation[7] is much more difficult than that of smaller rings because of unfavorable entropy and transannular interactions,[8] and the scope of the Conia and related reactions has been limited likely for the same reasons. To overcome these intrinsic mechanistic problems, we considered it necessary to find a powerful new reaction and reagent to achieve this goal. In(OTf)$_3$ was among the reagents that we examined first as it is the most powerful catalyst for an intermolecular version of the Conia reaction.[9] However, the In(OTf)$_3$-catalyzed reaction of ω-alkynyl-β-ketoester **1s** to form a six-membered ring was rather slow and afforded the desired product only in moderate yield even after 10 h at 100 °C with 1 mol% catalyst (Table 1, entry 1).

Table 1: In-catalyzed cyclization reaction of unsubstituted ω-alkynyl-β-ketoesters.



Entry[a]	Substrate, s	X	Conditions	Ring size	Product (ratio)	Yield [%][b]
1	**1s** (n = 0, R^2 = Et)	OTf	1 mol%, 0.1 M 100 °C, 10 h	6	**1b**	58
2	**1s** (n = 0, R^2 = Et)	NTf$_2$	1 mol%, 0.1 M 100 °C, 10 h	6	**1b**	90
3	**2s** (n = 1, R^2 = Me)	NTf$_2$	1 mol%, 0.1 M 100 °C, 2 h	7	**2b**+**2c** (38:62)	98
4	**2s** (n = 1, R^2 = Me)	NTf$_2$	0.1 mol%, 0.1 M 120 °C, 12 h	7	**2b**+**2c** (60:40)	81
5	**3s** (n = 2, R^2 = Me)	NTf$_2$	1 mol%, 0.1 M 120 °C, 12 h	8	**3c**	51
6	**4s** (n = 3, R^2 = Et)	NTf$_2$	1 mol%, 0.04 M 150 °C, 8 h	9	**4c**	7
7	**5s** (n = 9, R^2 = Me)	NTf$_2$	2 mol%, 0.01 M 150 °C, 18 h	15	**5b**[c]	27

[a] The initial cyclization product **a** isomerized in situ to give **b** and/or **c** and hence was not isolable. [b] Isolated yield. [c] The *endo* olefinic bond had exclusively *E* geometry (Scheme 2).

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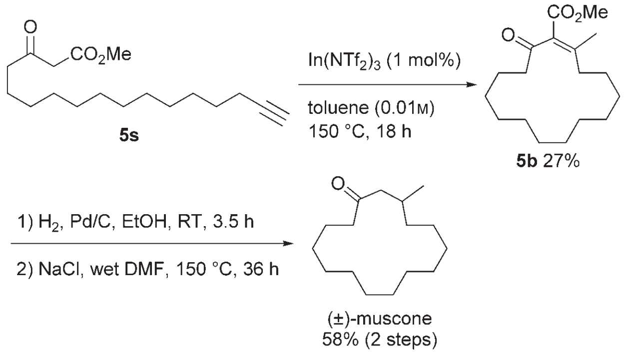
Screening of several indium salts indicated that 1 mol% of In(NTf$_2$)$_3$[10] produces the desired six-membered ring compound **1b** in 90% yield in 10 h at 100 °C (Table 1, entry 2).[11] The product was obtained as a conjugated *endo* olefinic enone **1b** (after in situ isomerization of the *exo* olefinic product **1a**). Interestingly, formation of the seven-membered ring from **2s** took place much faster than that of the six-membered ring (complete in 2 h under the same conditions) and in a better yield (98%; Table 1, entry 3). Even 0.1 mol% of In(NTf$_2$)$_3$ effectively catalyzed the reaction at 120 °C to afford the seven-membered-ring product in 81% yield. Formation of the eight-membered ring from **3s** took place more slowly and in a lower yield (51%; Table 1, entry 5). The structure of **3c** was confirmed by X-ray structure analysis.[12] Formation of the nine-membered ring from ω-alkynyl-β-ketoester **4s** was very slow even at 150 °C and gave the product **4c** in 7% yield (Table 1, entry 6).

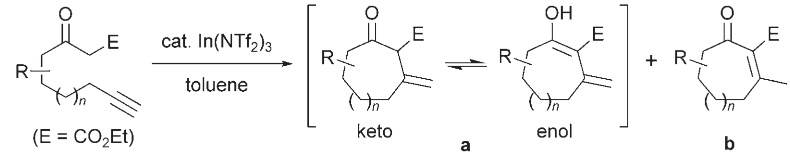
Formation of the fifteen-membered-ring from **5s** took place in a 0.01M toluene solution to give the product **5b** in 27% yield (Table 1, entry 7), while the formation of ten- and eleven-membered rings from the methylene homologues of **4s** was too slow to be useful. The product **5b** was transformed into (±)-muscone by hydrogenation followed by decarboxylation (Scheme 2).[4]

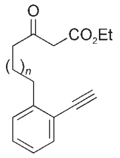
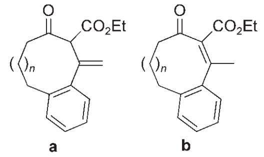
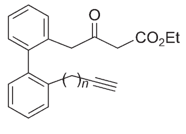
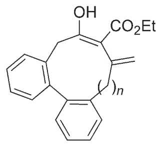
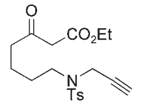
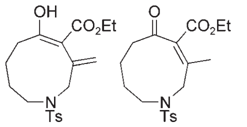


Scheme 2. Synthesis of (±)-muscone through the fifteen-membered ring product **5b**. DMF = *N*,*N*-dimethylformamide.

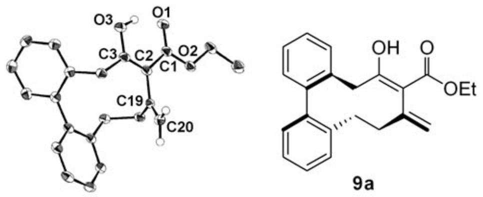
The method was found to be useful for the synthesis of medium-sized rings of some complexity at concentrations of 0.04–0.1M in toluene with In(NTf$_2$)$_3$ (1 mol%) at temperatures between 100 and 150 °C (Table 2). Note that some of the reactions were much faster than that to form the six-membered ring (compare with entry 2, Table 1). Not unexpectedly, the products were often obtained as a mixture of keto/enol and double-bond isomers. Phenylacetylenes **6s** and **7s** gave the corresponding benzo-fused eight- and nine-membered rings. Thus, **6s** cyclized quickly at 100 °C in 2 h to afford an isomeric mixture of benzocyclooctanone **6a** (exclusively in its keto form) and benzocyclooctenone **6b** in 75% combined yield (Table 2, entry 1). The formation of a nine-membered ring from **7s** took place more slowly but with a comparable yield of 71% to give an isomeric mixture of **7a** and **7b** (each consisting of isomers; see footnote for entry 2, Table 2). The reaction of **8s** quickly afforded a dibenzocyclooctane ring, a basic carbon skeleton of some lignans,[5] in 1 h in 89% yield (Table 2, entry 3). The product **8a** was obtained as a keto/enol tautomeric mixture (47:53). A crystalline dibenzocyclodecane **9a** was obtained in 74% yield exclusively in its enol form and as a single diastereomer (Table 2, entry 4). The stereochemistry of **9a** was confirmed by single-crystal X-ray structural analysis

Table 2: In(NTf$_2$)$_3$-catalyzed cyclization reaction of substituted ω-alkynyl-β-ketoesters.



Entry	Substrate	Conditions	Ring size	Product (ratio)	Yield [%][a]
					
1	**6s** (n=1)	1 mol%, 0.1 M 100 °C, 2 h	8	**6a**[b] + **6b** (23:77)	75
2	**7s** (n=2)	1 mol%, 0.05 M 120 °C, 12 h	9	**7a**[c] + **7b** (15:85)	71
					
3	**8s** (n=0)	1 mol%, 0.05 M 100 °C, 1 h	8	**8a**[d]	89
4	**9s** (n=2)	1 mol%, 0.05 M 100 °C, 8 h	10	**9a**[e]	74
					
5	**10s**	1 mol%, 0.05 M 150 °C, 1.5 h	9	**10a**[f] + **10b** (85:15)	61

[a] Isolated yield. [b] Keto 100%. [c] Keto/enol = 11:89. [d] Keto/enol = 47:53; keto: major/minor = 90:10; enol: major/minor = 94:6. The origin of the isomerism in the keto form is due to the central chirality at the α-position of the ester moiety and the axial chirality of the biphenyl moiety. The enol form does not have any central chirality, and the observed isomer may be due to the axial chirality at the biphenyl and the butadiene moieties (see Figure 1). [e] Enol 100%. [f] Keto/enol = 34:66.



9a

Figure 1. ORTEP drawing of the ten-membered ring product **9a** (50% probability for thermal ellipsoids). Hydrogen atoms except for those on O3 and C20 are omitted for clarity. 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).

(Figure 1).[12] A nine-membered ring compound **10p** bearing an *N*-*p*-toluenesulfonyl moiety was synthesized in 61% yield from a ketoester **10s** (Table 2, entry 11). The reaction required the use of 10 mol% In(NTf$_2$)$_3$ to suppress the loss of the ethoxycarbonyl group that occurred competitively in the reaction under a lower (1 mol%) catalyst loading.

In conclusion, we have developed an In(NTf$_2$)$_3$-catalyzed cycloisomerization of ω-alkynyl-β-ketoesters that produces six- to fifteen-membered all-carbon- or nitrogen-containing rings through an intramolecular metalla ene reaction between an indium enolate and an acetylenic bond. The reaction features the following: 1) a relatively low catalyst loading, 2) good atom efficiency, 3) the requirement of only moderately dilute reaction conditions, and 4) an anomalous relationship between the ring size and the cyclization rate. The efficiency of the present catalytic system is attributed to a dual activation of both enolate and acetylenic moieties, as shown by our previously reported computational transition-state model of the intermolecular reaction; The indium enolate of a 1,3-dicarbonyl compound and an acetylene group forms a well-ordered bicyclo[2.2.2]octane-type structure, which forces the substituents on the reactants to point toward certain restricted directions.[9d] We therefore consider that it is this directionality that made the reaction suitable for the formation of medium-sized rings, thus allowing the reaction to take place cleanly at a rather high concentration with a relatively small amount of the catalyst for a rather wide range of substrate variations.

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[11] Attempted five-membered-ring formation gave furan derivatives due to an oxygen-centered cyclization reaction.

[12] CCDC-649749 (**3c**) and 649750 (**9a**) contain 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.