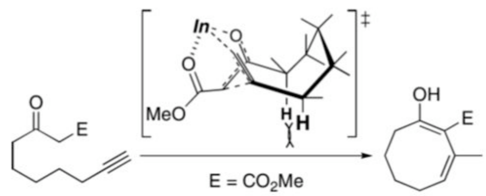
Efficient Formation of Ring Structure Utilizing Multisite Activation by Indium Catalysis

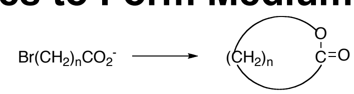


Yoshimitsu Itoh, Hayato Tsuji, Ken-ichi Yamagata, Kohei Endo, Iku Tanaka,
Masaharu Nakamura, Eiichi Makamura

J. Am. Chem. Soc, **2008**, 130 (50), 17161-17167

Wipf Group Current Literature
Tingting Mo
Dec, 20, 2008

Ease of Ring Closure Reactions of Bifunctional Chain Molecules to Form Medium-sized Rings



$CH_3(CH_2)CO_2^- + CH_3(CH_2)_nBr \longrightarrow CH_3CH_2CH_2CO_2(CH_2)_nCH_3$

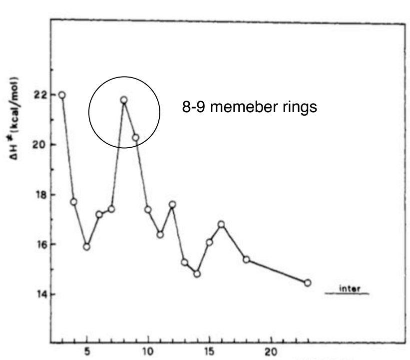


Figure 4. $\Delta H^{\ddagger}$ profile for the formation of lactones (eq 4).

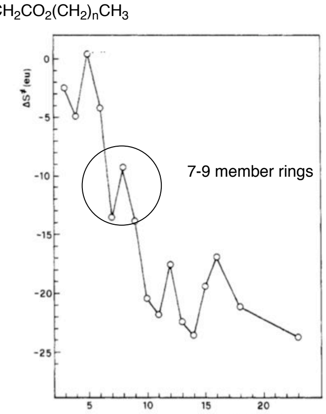


Figure 6. $\Delta S^{\ddagger}$ profile for lactone formation (eq 4).

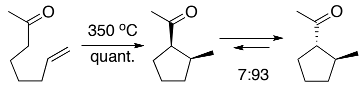
Ring strain arises from 1) bond position forces due to imperfiect staggering
2) deformation of ring bond angles
3) transannular strains due to repulsive interactions between atoms across the ring

Strains 1) and 3) are especially severe for medium-ring cycloalkanes

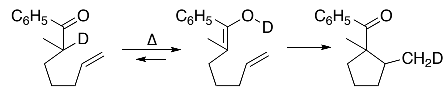
Usually reactions in low concentrations to prevent polymerization

Illuminari, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95-102
Galli, C.; Mandolini, L. *Eur. J. Org. Chem.* **2000**. *100*, 2963-3007

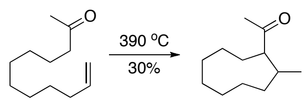
Conia-ene Cyclization



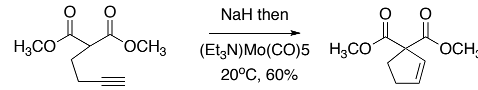
F. Rouessac, R. Beslin, J. M. Conia. *Tetrahedron Lett.* **1965**, 3319



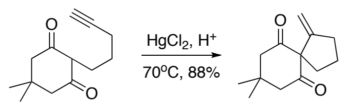
P. Le Perchec, F. Rouessac. J. M. Conia. *Bull. Soc. Chim. France.* **1967**. 830



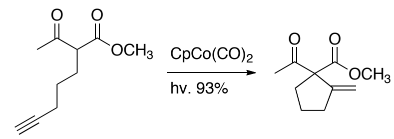
J. M. Conia, J. Leyendecker, C. Dubois-Faget. *Tetrahedron Lett.* **1966**, 129



McDonald, F. E.; Olson, T. C. *Tetrahedron Lett.* **1997**, *38*, 7691

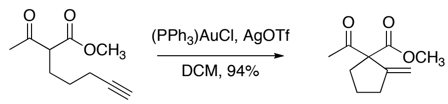


Boaventura, M. A.; Drouin, J.; Conia, J. M. *Synthesis*, **1983**, 801



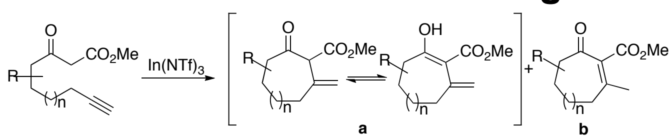
Cruciani, P.; Stammler, R.; Aubert, C.; Malacria, M. *J. Org. Chem.* **1996**, *61*, 2699

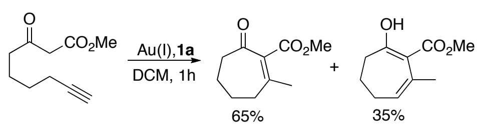
Neutral condition
Ambient temperature

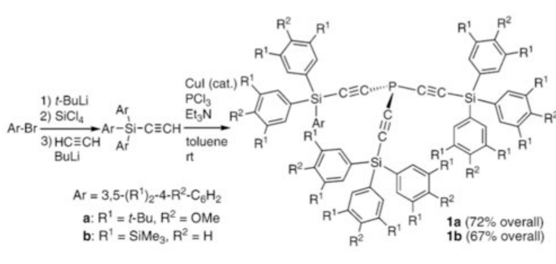


Kennedy-Smith, J. J.; Staben, S. T.; Toste, F. D. *J. Am. CHem. Soc.* **2004**, *126*. 4526

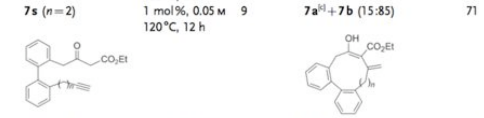
Conia-ene Cyclization to Form Medium-Sized rings





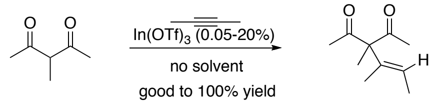


Ochida, A.; Ito, H.; Savamura, M. *J. Am. Chem. Soc.* **2006**, *128*, 16486

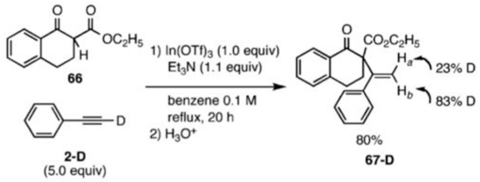
Entry	Substrate	Conditions	Ring size	Product (ratio)	Yield [%][a]
					
1	**6s** ($n=1$)	1 mol%, 0.1 M 100°C, 2 h	8	**6a**[b] + **6b** (23:77)	75
2	**7s** ($n=2$)	1 mol%, 0.05 M 120°C, 12 h	9	**7a**[c] + **7b** (15:85)	71
					
3	**8s** ($n=0$)	1 mol%, 0.05 M 100°C, 1 h	8	**8a**[d]	89
4	**9s** ($n=2$)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

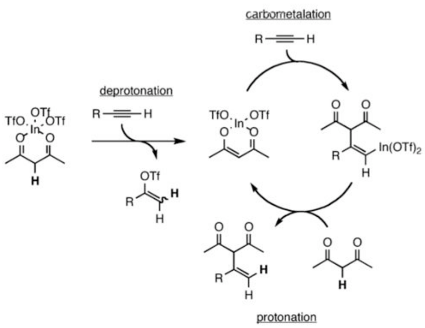
Tsuji, H.; Yamagata, K.; Itoh, Y.; Endo, K.; Nakamura, M.; Nakamura, E.
Angew. Chem. Int. Ed. **2007**, *47*, 6244

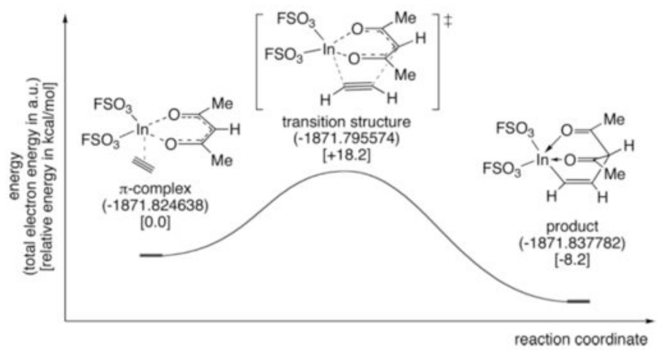
Mechanism of Indium Catalyzed 2-Alkenylation of 1,3-dicarbonyl compounds with Unactivated Alkynes



1) high catalytic efficiency
2) high yield
3) no solvent
4) high atom economy



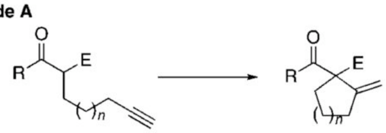




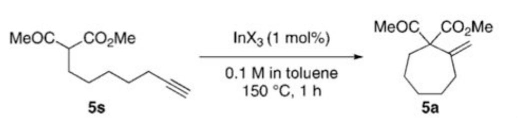
Interaction between Indium and aceylene
Multisite activation

Endo, K.; Hatakeyama, T.; Nakamura, M.; Nakamura, E, *J. Am. Chem. Soc,* **2007**, *129,* 5264

Indium Catalyzed Conia-ene Cyclization: Mode A

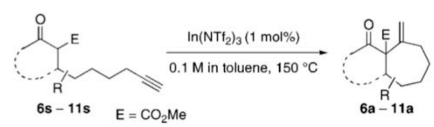


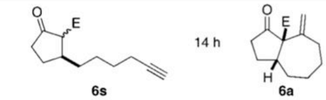
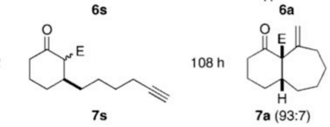
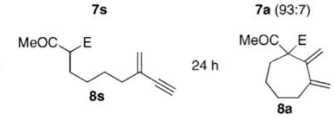
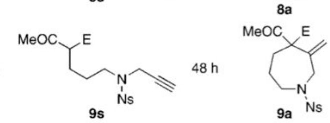
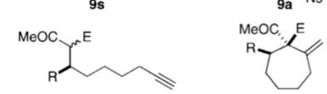
α-(ω′-Alkynyl)-β-ketoesters



entry	X	yield[a]
1	OTf	40%
2	ONf	67%
3	NTf_2	75%
4	NTf_2	93%[b]
5	Cl	0%

1) NTf_2 is the best catalyst because of the steric bulkness to prevent the deactivation of the indium metal by extra coordination
2) No reaction took place in a coordinative solvent such as THF or DMF

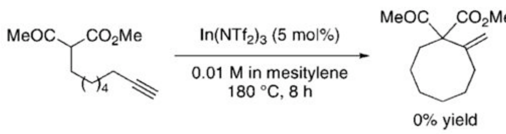


entry	substrate	reaction time	product[a]	total yield[b]
1	 6s	14 h	6a	81%
2	 7s	108 h	7a (93:7)	84%
3	 8s	24 h	8a	91%
4	 9s	48 h	9a	83%
5	 10s (R = Et)	36 h	10a (93:7)	85%
6	11s (R = Ph)	1 h	11a (96:4)	94%

Frost, C. G.; Hartley, J. P.; Griffin, D. *Tetrahedron Lett.* **2002,** *43*, 4789

Itoh, Y.; Tsuji, H.; Yamagata, K.; Endo, I. T.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2008***, 130*, 17161

Indium Catalyzed Conia-ene Cyclization: Mode B



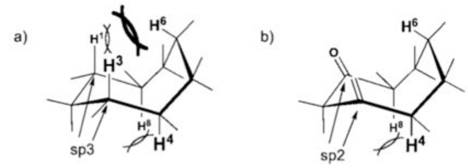
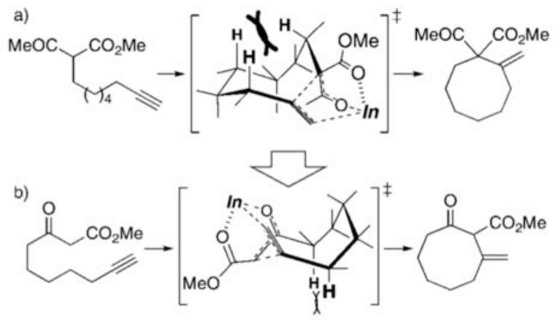


Figure 5. Schematic representations of eight-membered rings: (a) cyclooctane; (b) 3-methylenecyclooctanone.



Severe transannular interaction in cyclooctane
Replacement of sp^3 to sp^2 carbon atoms to reduce the strain

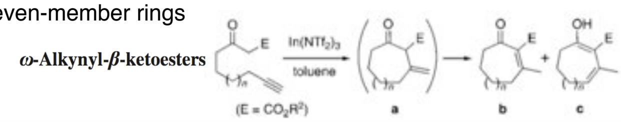
Substitution of a $-CH_2CH_2-$ group by a *cis* double bond reduces the strain energy of cyclooctane by 2.7 kcal/mol
Allinger, N. L.; Sprague, J. T.; *J. Am. Chem. Soc.* **94**, 5734

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).

Itoh, Y.; Tsuji, H.; Yamagata, K.; Endo, I. T.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 17161

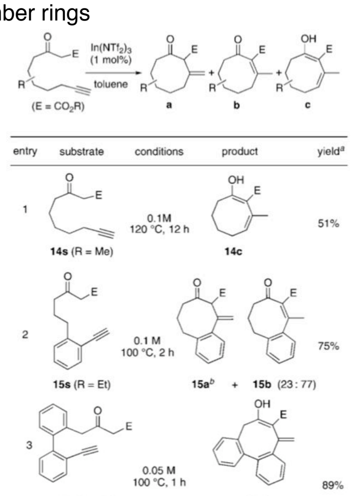
Indium Catalyzed Conia-ene Cyclization: Mode B

Six- and seven-member rings

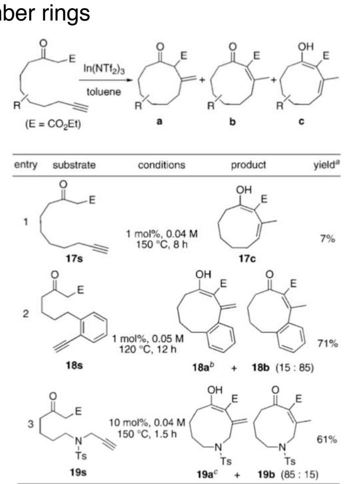


entry[a]	substrate	conditions	product[b]	total yield[c]
1	**12s** (n = 0, R^2 = Et)	1 mol %, 0.1 M, 100 °C, 10 h	**12b** (6)	90%
2	**13s** (n = 1, R^2 = Me)	1 mol %, 0.1 M, 100 °C, 2 h	**13b** + **13c** (7) (38: 62)	98%
3	**13s** (n = 1, R^2 = Me)	0.1 mol %, 0.1 M, 120 °C, 12 h	**13b** + **13c** (7) (60: 40)	81%

Eight-member rings



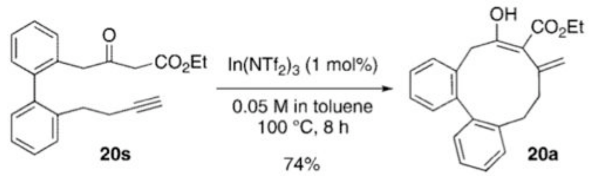
Nine-member rings



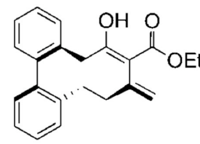
Itoh, Y.; Tsuji, H.; Yamagata, K.; Endo, I. T.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 17161

Indium Catalyzed Conia-ene Cyclization: Mode B

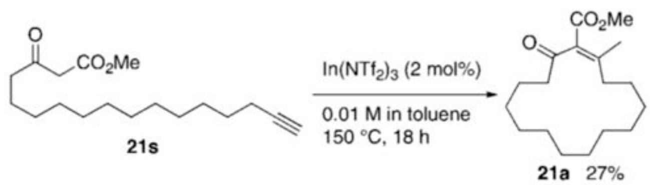
Ten-member ring



one diastereomer



Fifteen-member ring



Itoh, Y.; Tsuji, H.; Yamagata, K.; Endo, I. T.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 17161

Conclusion

a) The use of Indium(III) catalyst, in particular $In(NTf_2)_3$
This catalyst organize the transition state of the cyclization by means of multisite interactions
Allow the system to overcome the entropy and enthalpy barriers in the formation of medium- to large-sized rings

b) With careful disign of substrates to reduce transannular steric interactions, the mode B type of substrates readily gave medium- to large-sized rings while the mode A type substrates are the best for five-membered rings.

c) Low catalyst loading, as low as 0.01 mol% in the best case
No solvent for five-member-ring formation
Only moderately dilute reaction conditions for medium-sized-ring formation
High atom economy