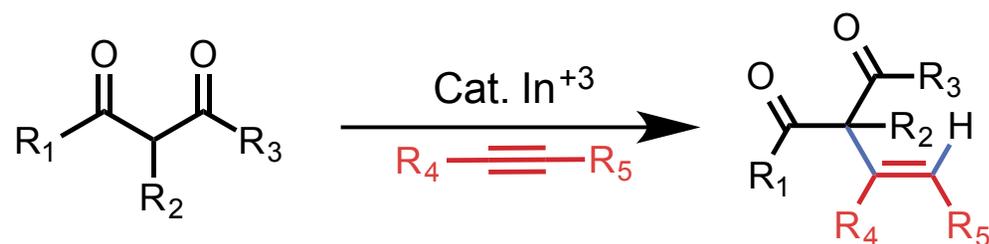
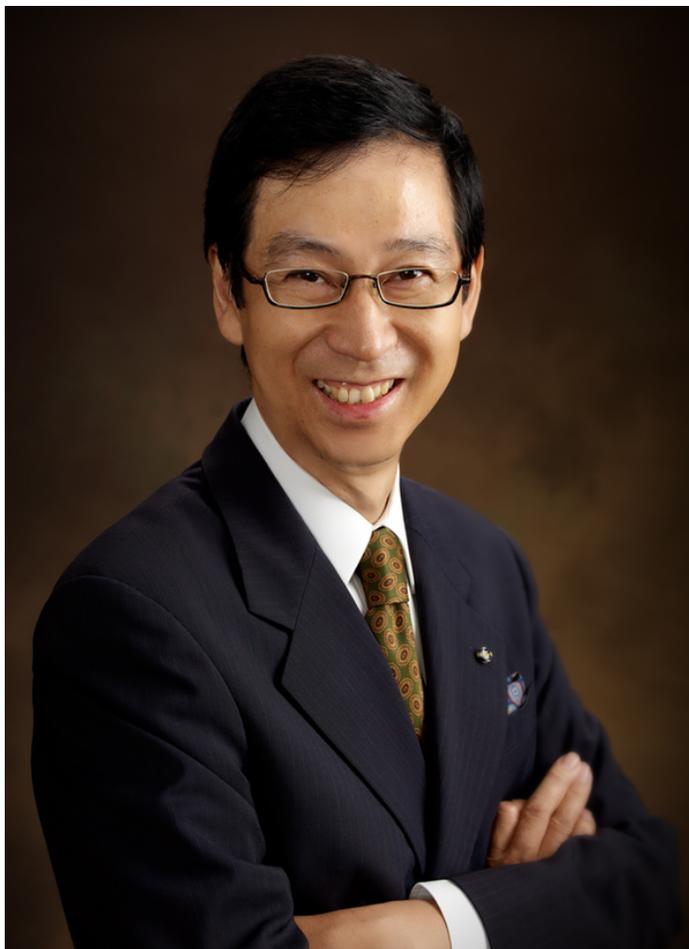


ENOLATE ADDITIONS TO ALKYNES: THE NAKAMURA REACTION



BRAD GILBERT
DENMARK GROUP MEETING
APRIL 29, 2014

EIICHI NAKAMURA



**University of Tokyo:
Chairman, Dept. of
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Born 1951 in Tokyo

**B.S. (T. Mukaiyama),
Ph.D. (I. Kuwajima) at
Tokyo Inst. of Tech.**

**Post Doc. at Columbia
(G. Stork)**

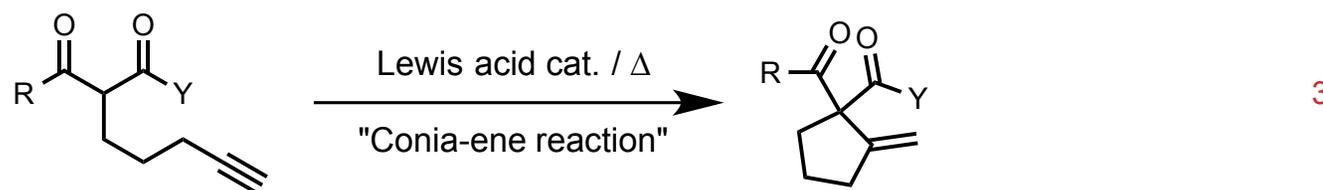
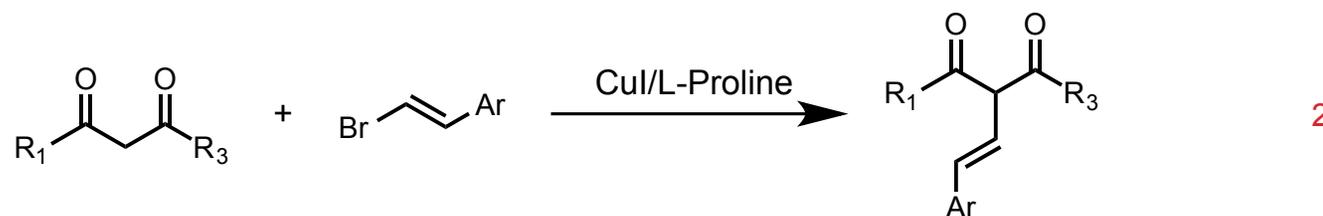
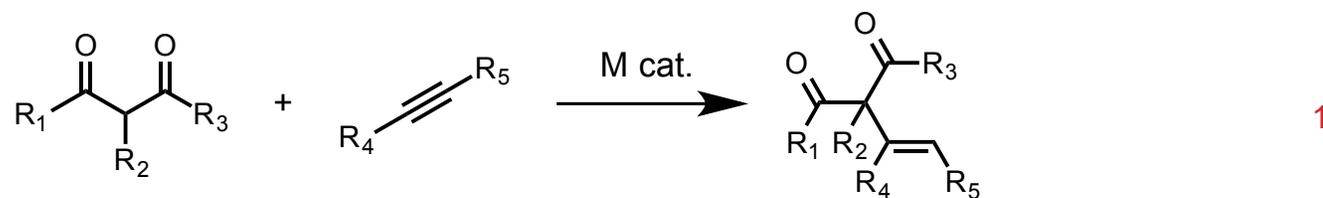
JACS associate editor

>400 publications

OUTLINE

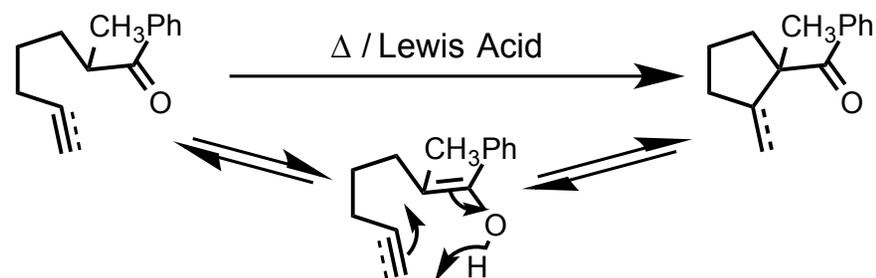
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 - Zinc enolate additions to alkynes
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 - Modular synthesis
 - Total synthesis

INTRODUCTION: VINYLATION OF ACTIVE METHYLENES

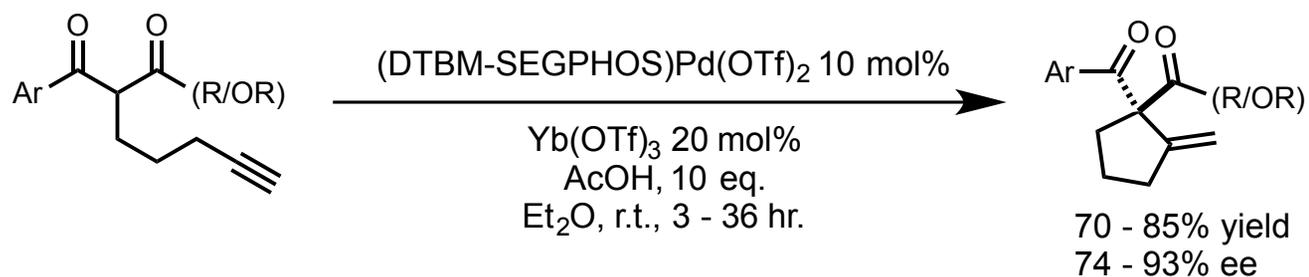


- 1: (Iridium) Endo, K.; Hatakeyama, T.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2007**, *129*, 5264. (Rhenium) Kuninobu, Y.; Kawata, A.; Takai, K. *Org. Lett.*, **2005**, *7*, 4823.; (Iridium) Onodera, G.; Kato, M.; Kawano, R.; Kometani, Y.; Takeuchi, R. *Org. Lett.*, **2009**, *11*, 5038.
2: Qian, W.; Pei, L. *Synlett*, **2006**, *11*, 1719.
3: (Rhenium) Kuninobu, Y.; Kawata, A.; Takai, K.; *Org. Lett.*, **2005**, *7*, 4823. (Nickel/Ytterbium) Gao, Q.; Zheng, B.-F.; Li, J.-H.; Yang, D. *Org. Lett.*, **2005**, *7*, 2185. (Palladium/Ytterbium)[enantioselective] Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.*, **2005**, *127*, 17168.

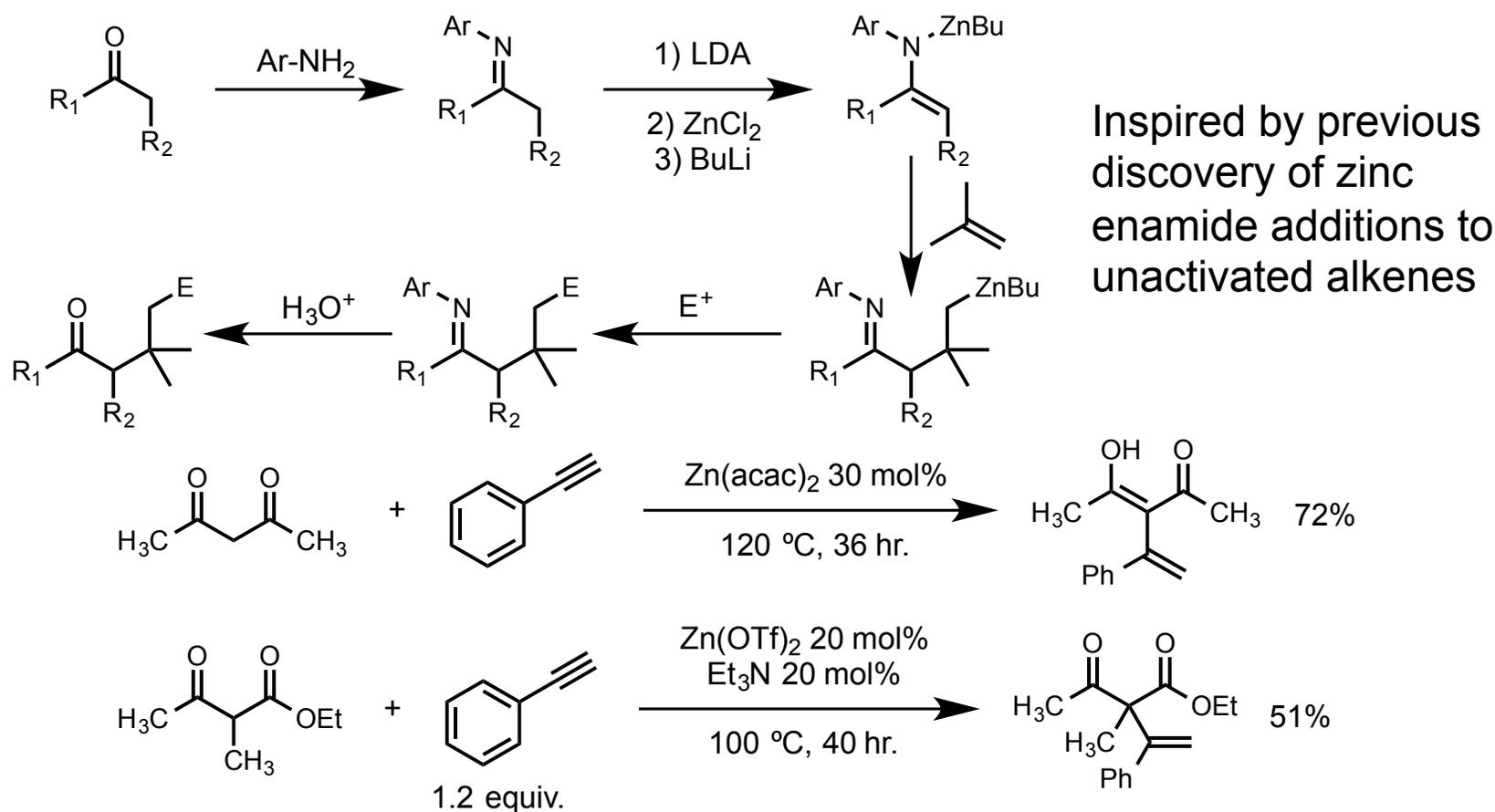
INTRODUCTION: THE CONIA-ENE REACTION



- Pericyclic [1,5]
- Thermal reaction infrequently utilized
- Some enantioselective applications (Toste)



ZINC ENOLATE ADDITIONS TO ALKYNES: DISCOVERY OF THE NAKAMURA REACTION

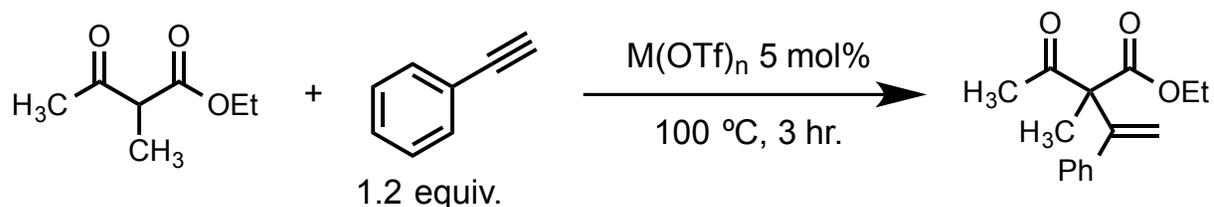


“We felt it necessary to find metal counteractions more powerful than zinc...”

Nakamura, M.; Hatakeyama, T.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 11820.

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

CATALYST SCREENING

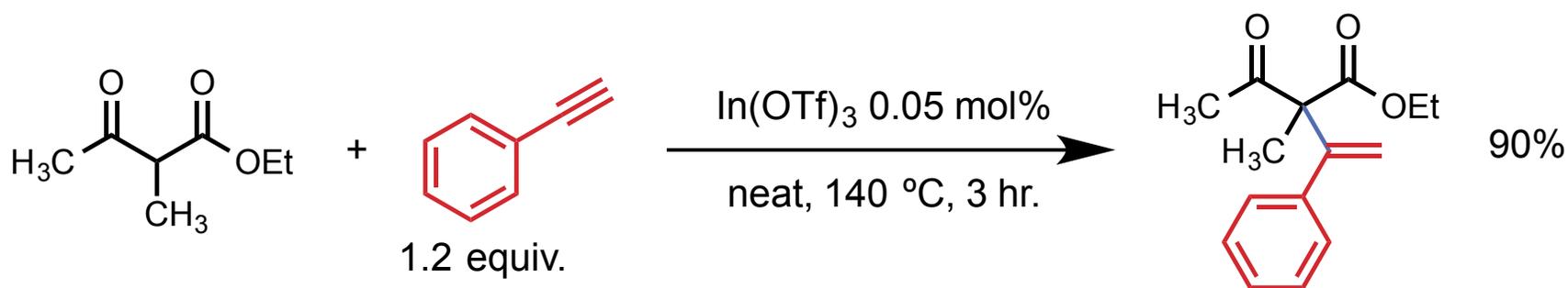


Metal triflate 5 mol%	Yield (3 hrs.)	Catalyst 5 mol%	Additive 15 mol%	Yield (12 hrs.)
Hg(OTf) ₂	3%	InCl ₃	--	0%
Al(OTf) ₃	0%	InCl ₃	AgOTf	80%
Ga(OTf) ₃	14%	--	AgOTf	6%
In(OTf) ₃	100%	In(OTf) ₃	--	100%
		In[N(Tf) ₂] ₃	--	100%*
		*6 hrs.		

OUTLINE

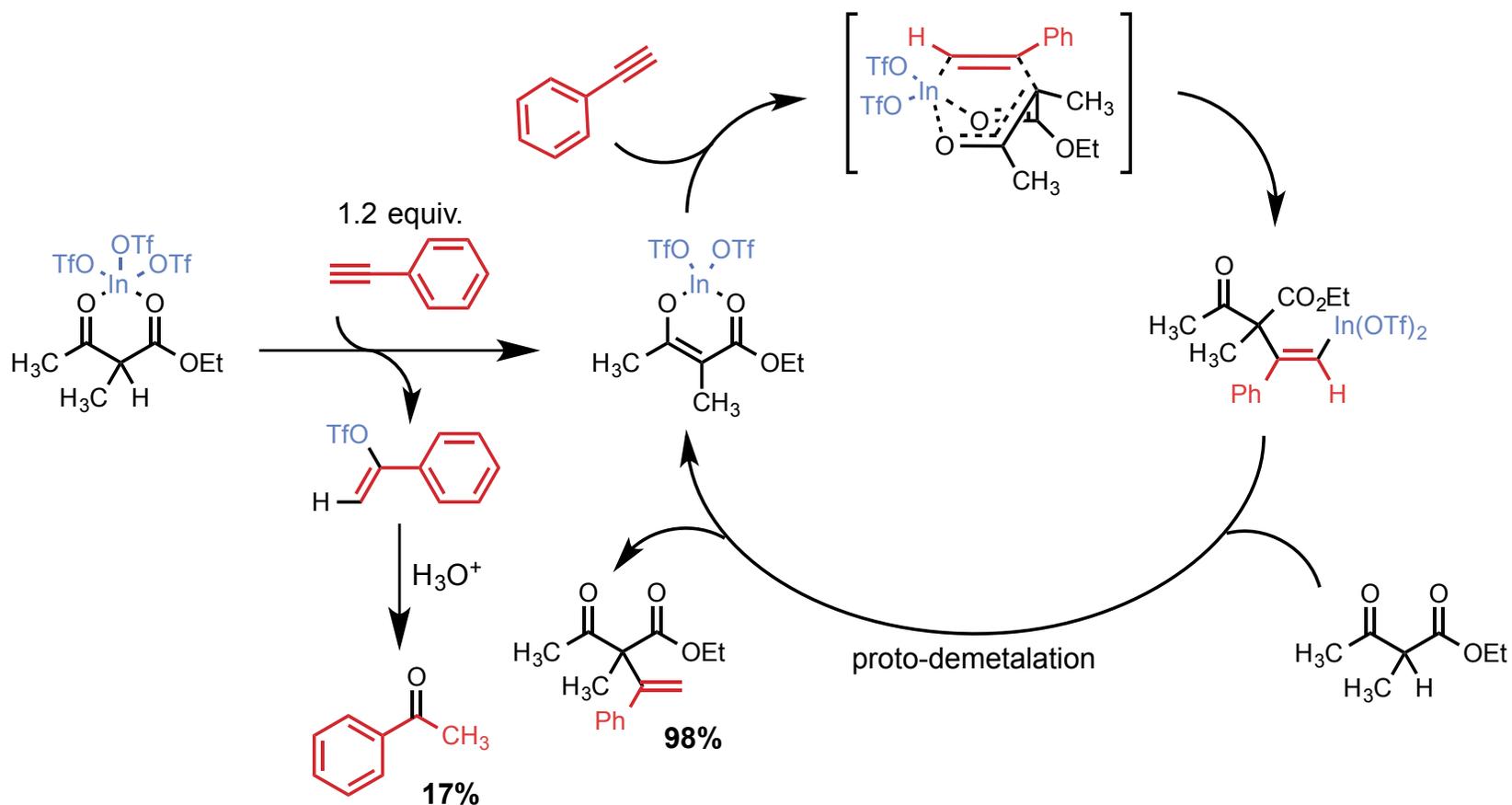
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THE NAKAMURA REACTION: A REPRESENTATIVE EXAMPLE



- **90-93% yield**
- **Forms a large variety of quaternary centers in excellent yield**
- **“Perfect” selectivity for the 1,1-disubstituted alkene**
- **The alkyne serves a purpose in trapping triflic acid released during catalyst activation, necessitating a slight excess**

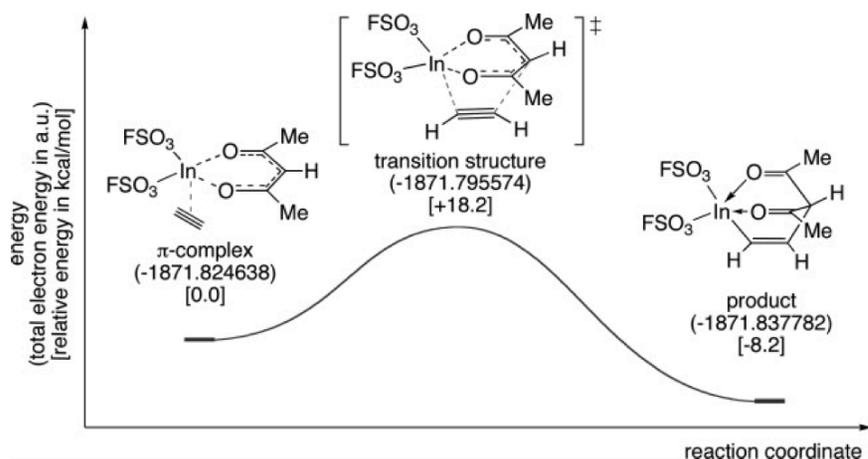
THE NAKAMURA REACTION: MECHANISM



20 mol% $\text{In}(\text{OTf})_3$, ambient temperature, 16 hours.

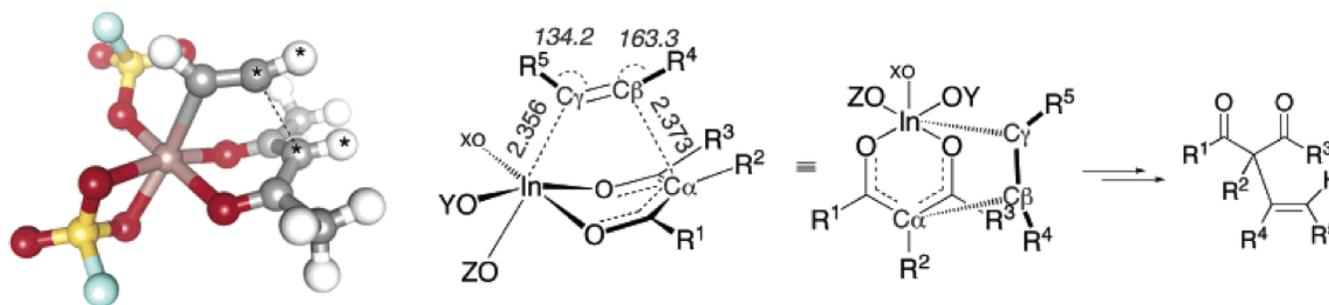
Endo, K.; Hatakeyama, T.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2007**, *129*, 5264.

MECHANISM: COMPUTATIONAL STUDIES OF THE T.S.



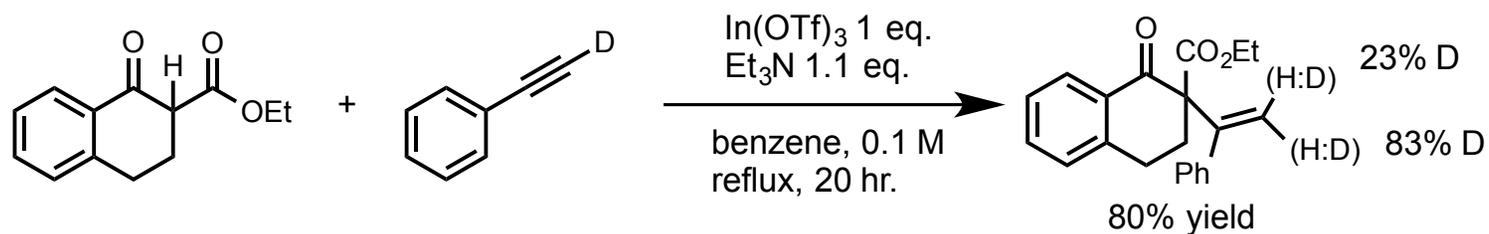
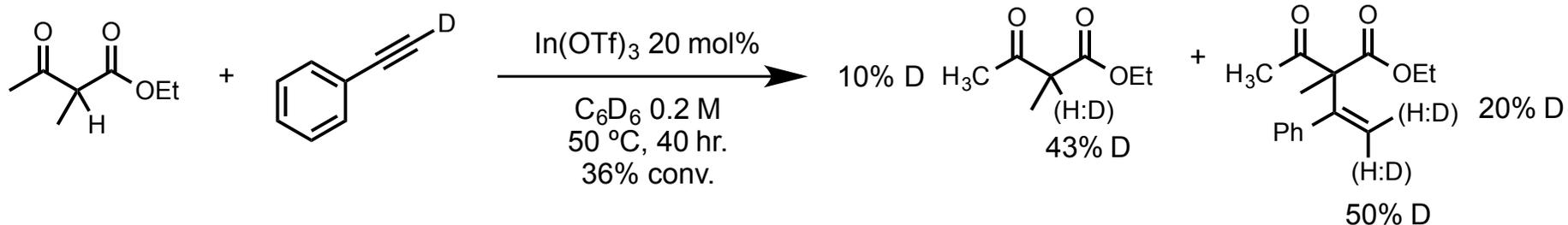
Noteworthy features:

- Advanced formation of the C-In bond over the C-C bond
- Plane of symmetry containing the indium, methylene and alkyne.

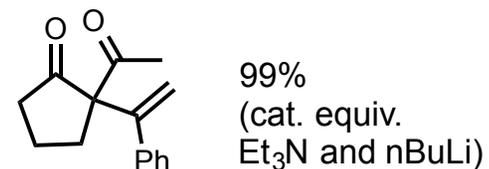
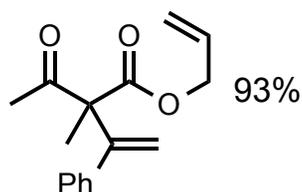
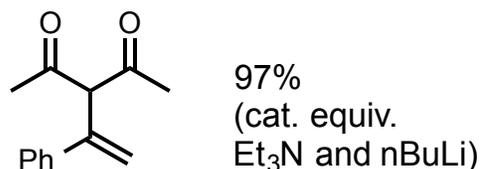
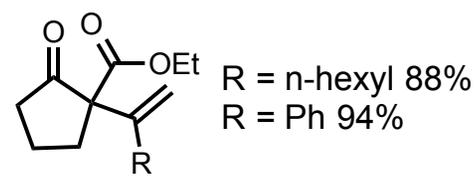
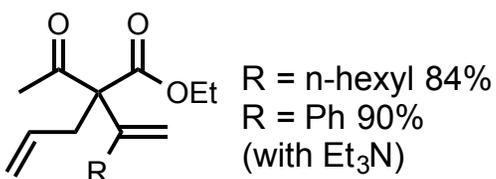
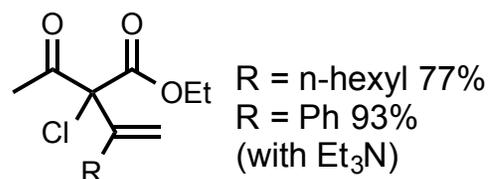
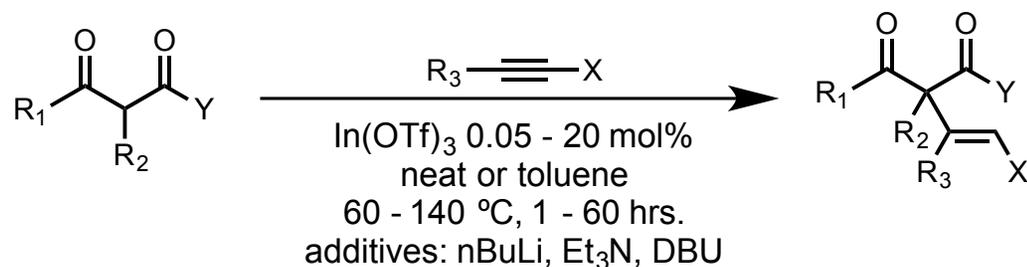


Basis sets: B3LYP/6-31G* and LANL2DZ for In

MECHANISM: DEUTERIUM LABELING STUDIES

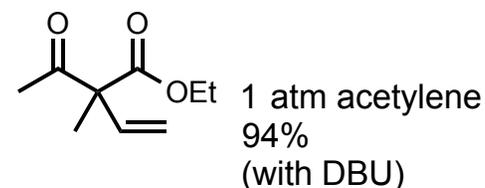
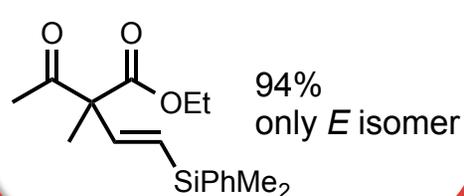
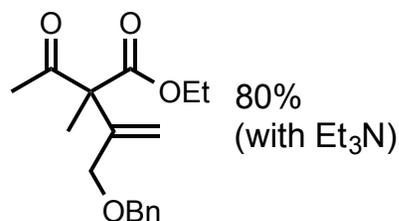
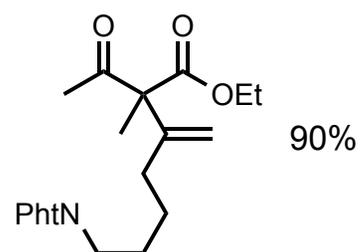
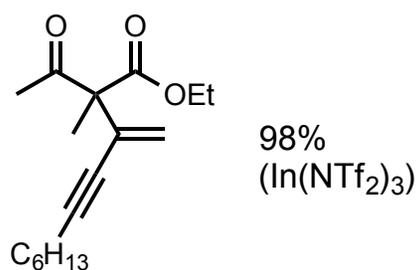
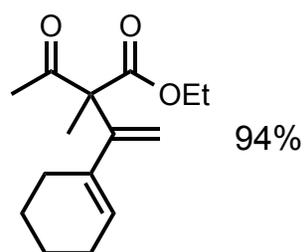
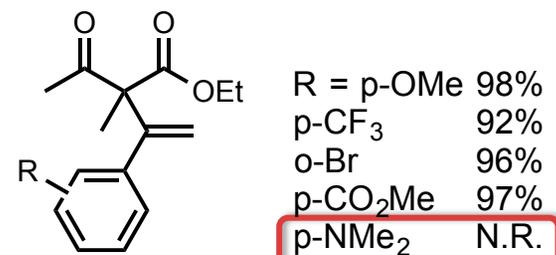
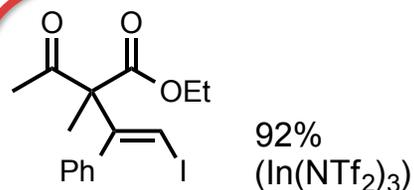
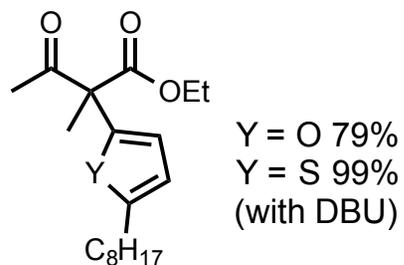


THE NAKAMURA REACTION: ASSESSMENT OF SCOPE



- Acid sensitive substrates saw improved yield with the addition of catalytic base

THE NAKAMURA REACTION: ASSESSMENT OF SCOPE



- Tolerates alkenes, benzyl and allyl ethers, phthalimides, esters, silanes, furans/thiophenes, and halides.
- Acid sensitive substrates saw improved yield with the addition of catalytic base
- Difficult substrates generally gave better yields with the triflimide (and at lower temperatures)

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

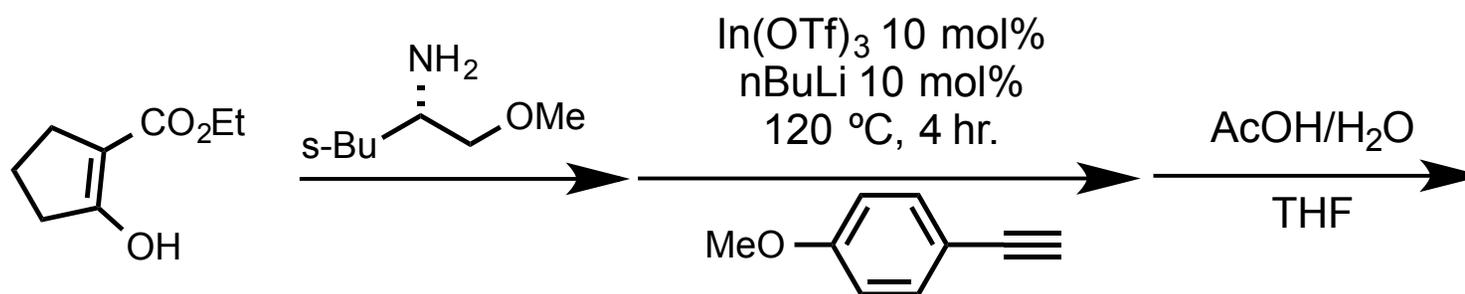
LIMITATIONS OF THE METHODOLOGY

- **Indium triflate catalysis is applicable to a broad range of dicarbonyls and alkynes, however:**
 - Conditions are highly variable (solvent, time, temperature, additives)
 - High temperatures are generally necessary
 - (Cheaper) indium salts other than the triflate and the triflimide are unreactive
- **Conversely:**
 - Catalyst loadings can be as low as 0.05 mol%
 - Ligandless
 - Perfect selectivity for terminal alkynes
 - Highly general formation of 1,1-disubstituted alkenes

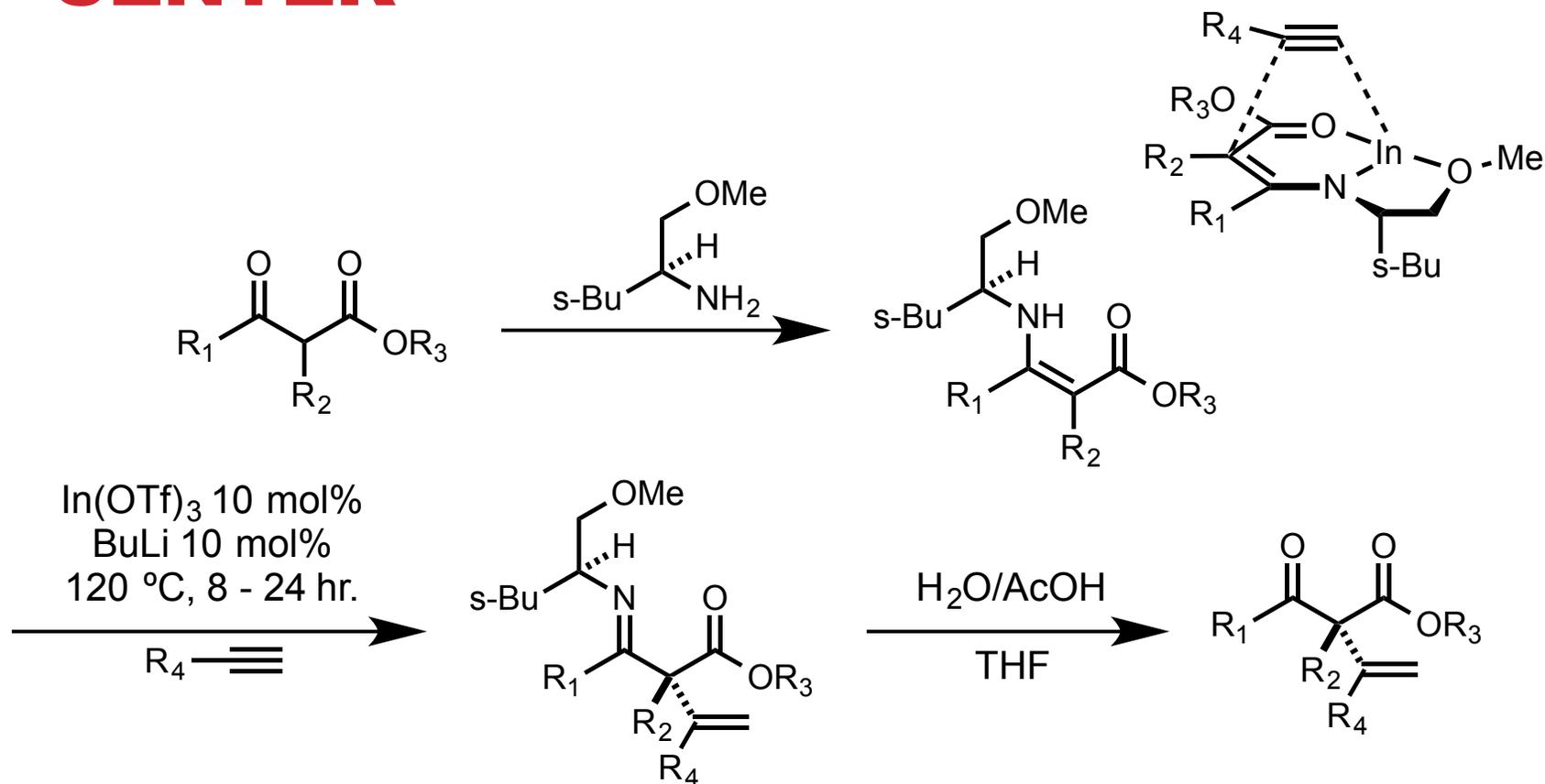
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GROUP PROBLEM: ENANTIOSELECTIVE REACTION



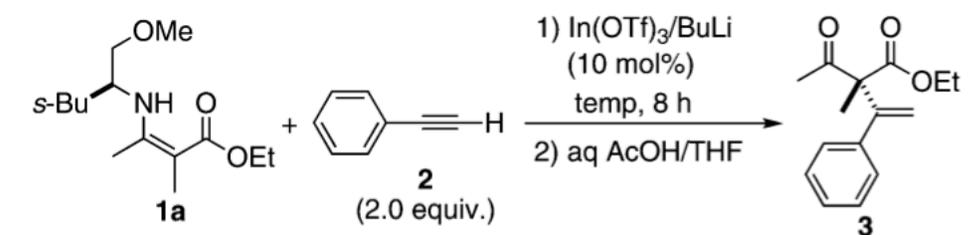
ENANTIOSELECTIVE ADDITIONS: FORMING A CHIRAL QUATERNARY CENTER



- nBuLi was an additive for all enantioselective reactions

STEREOSELECTIVE AT HIGH TEMPERATURES

Table 2. Temperature Effect on Stereoselectivity



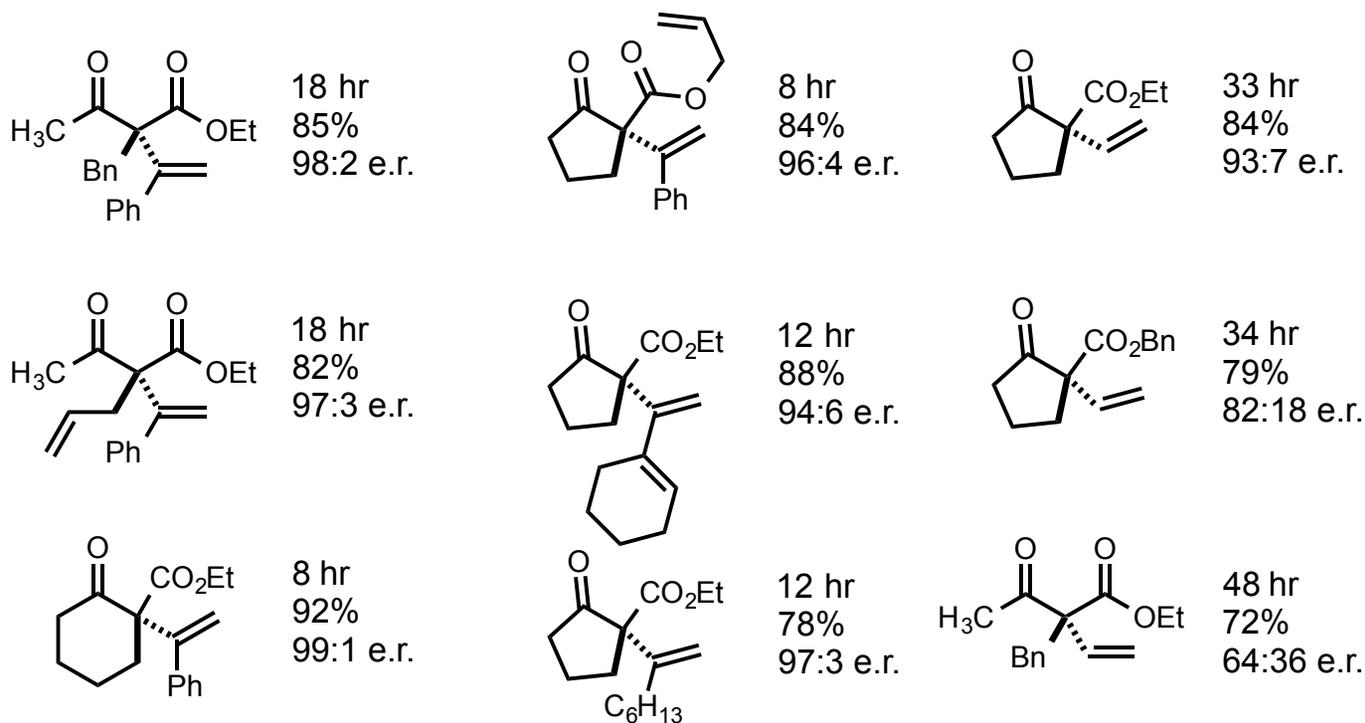
Entry	temp (°C)	% yield ^a	% ee ^b
1	70	87	68
2	100	94	83
3	120	92	94
4	140	93	91

“Such a temperature effect suggests that the selectivity is controlled by an entropy factor.”

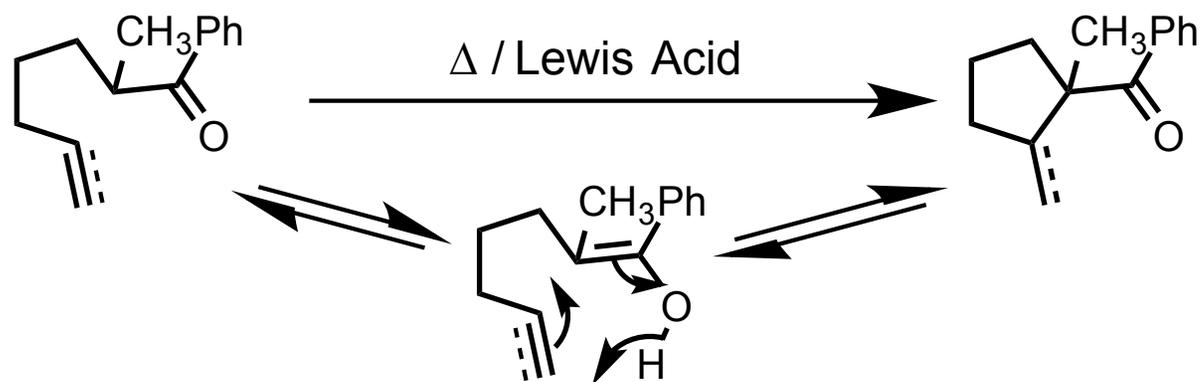
ENANTIOSELECTIVE SCOPE

Conditions:

- 1) $\text{In}(\text{OTf})_3$ 10 mol%,
BuLi 10 mol%,
120 °C, 8 – 24 hr.
- 2) $\text{H}_2\text{O}/\text{HOAc}$, THF

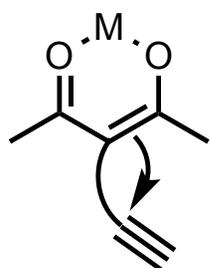


THE CONIA-ENE REACTION

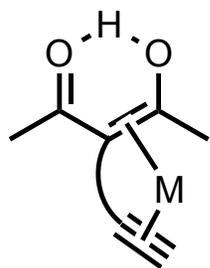


THE CONIA-ENE REACTION

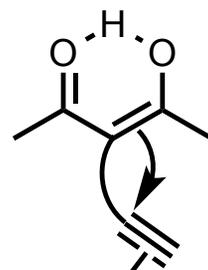
Nakamura proposes metal-dependent modes of Conia-ene substrate activation. In his model, only Indium activates both the alkyne and the enolate.



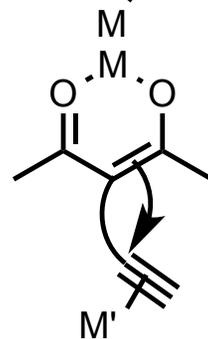
“Enol” activation
M = Sn, Ti



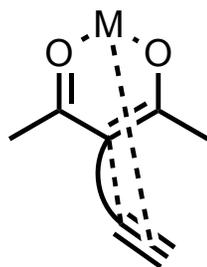
Ene-yne activation
M = Ni, Co, Re



Alkyne activation
M = Pd, Au



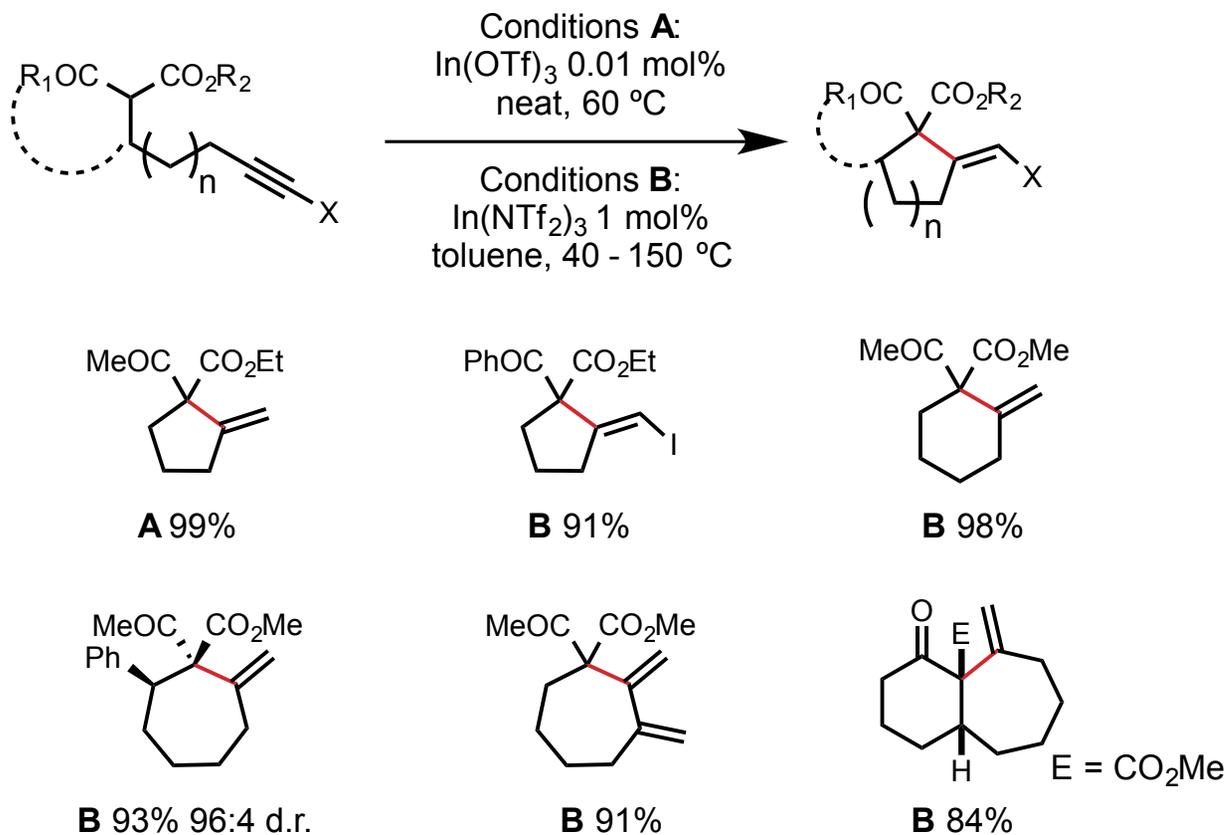
Two metals
M, M' = (Ag, Cu);
(K, Cu); (Pd, Yb)*



Double Activation by
one metal
M = In

*Toste – Pd(SEGPHOS)

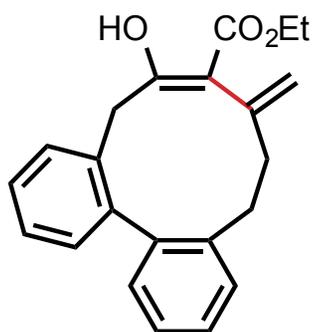
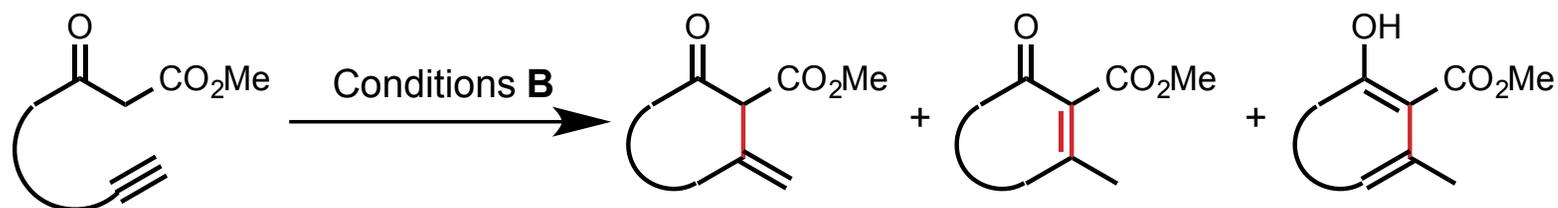
FORMATION OF MEDIUM-SIZED RINGS



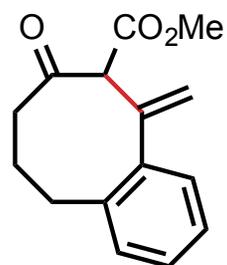
Consistent with the *syn*-carbometalation and internal selectivity of the intermolecular variant. Larger rings undergo double bond isomerization.

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

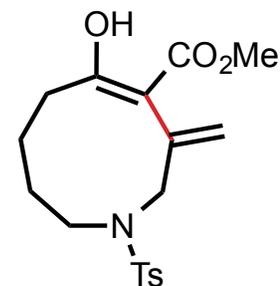
FORMATION OF MEDIUM-SIZED RINGS



74%



75%
23:77 exo:endo

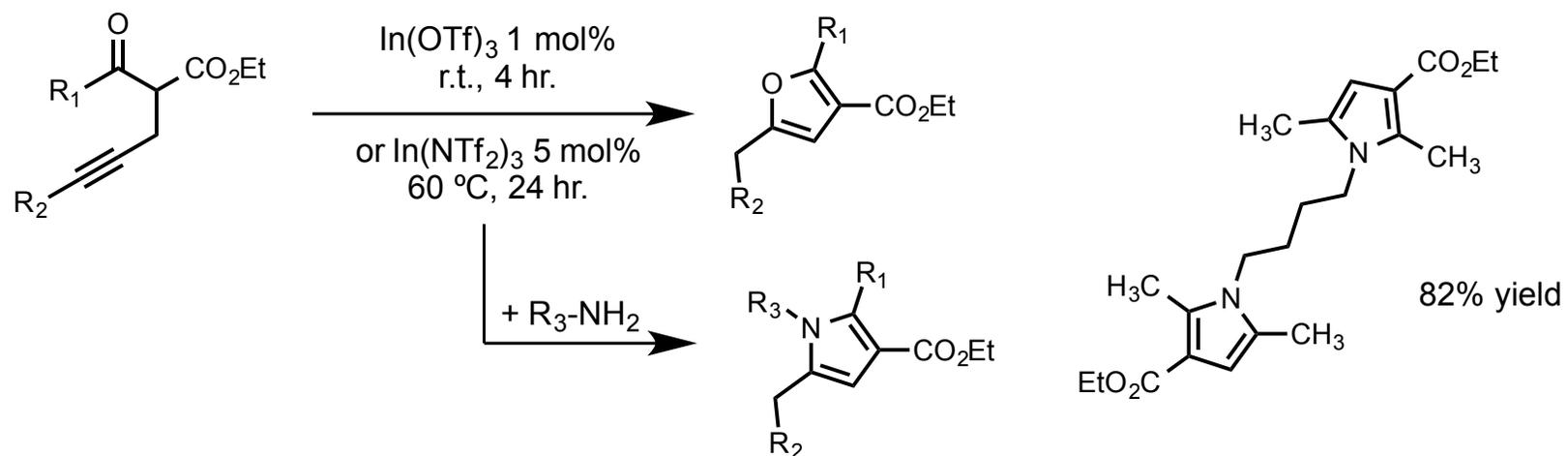


61%
85:15 exo:endo

Consistent with the *syn*-carbometalation and internal selectivity of the intermolecular variant. Larger rings undergo double bond isomerization.

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

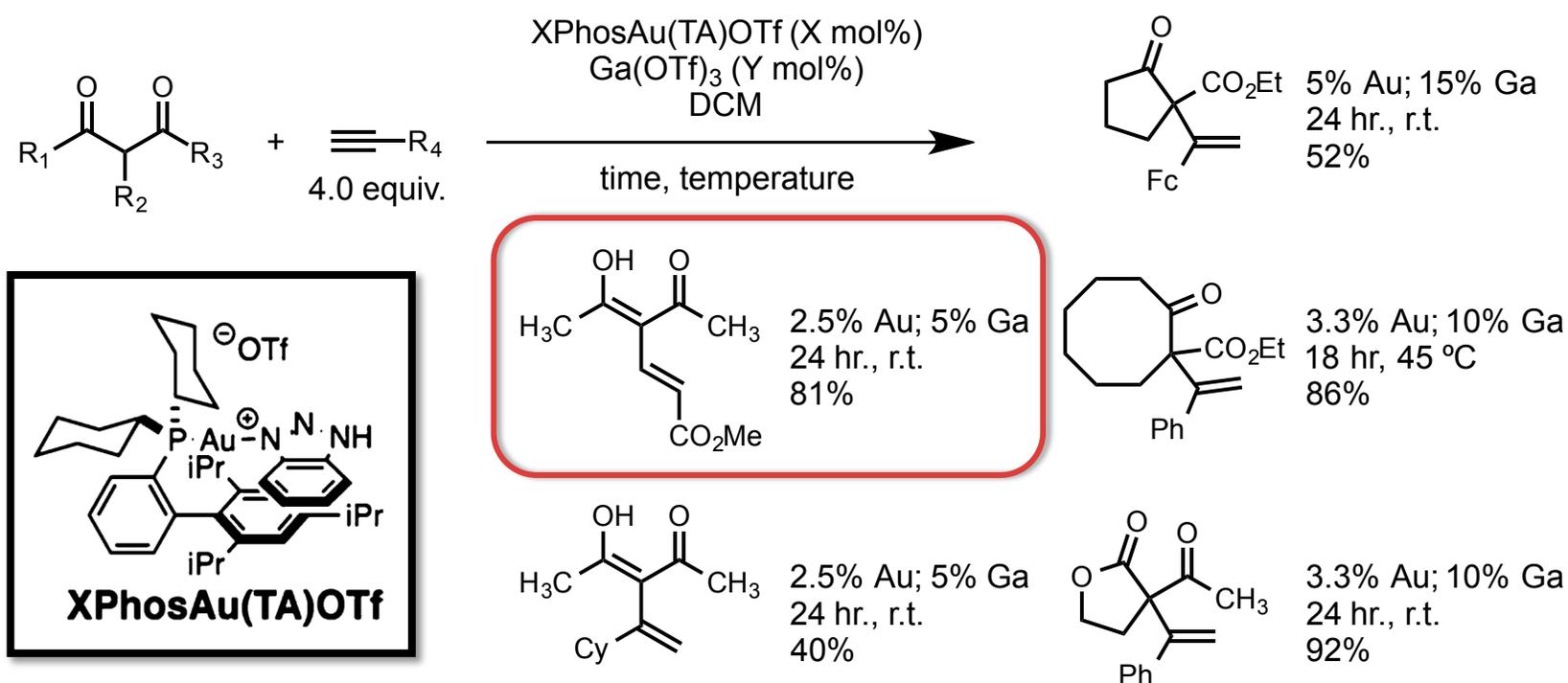
SHORTENING THE TETHER



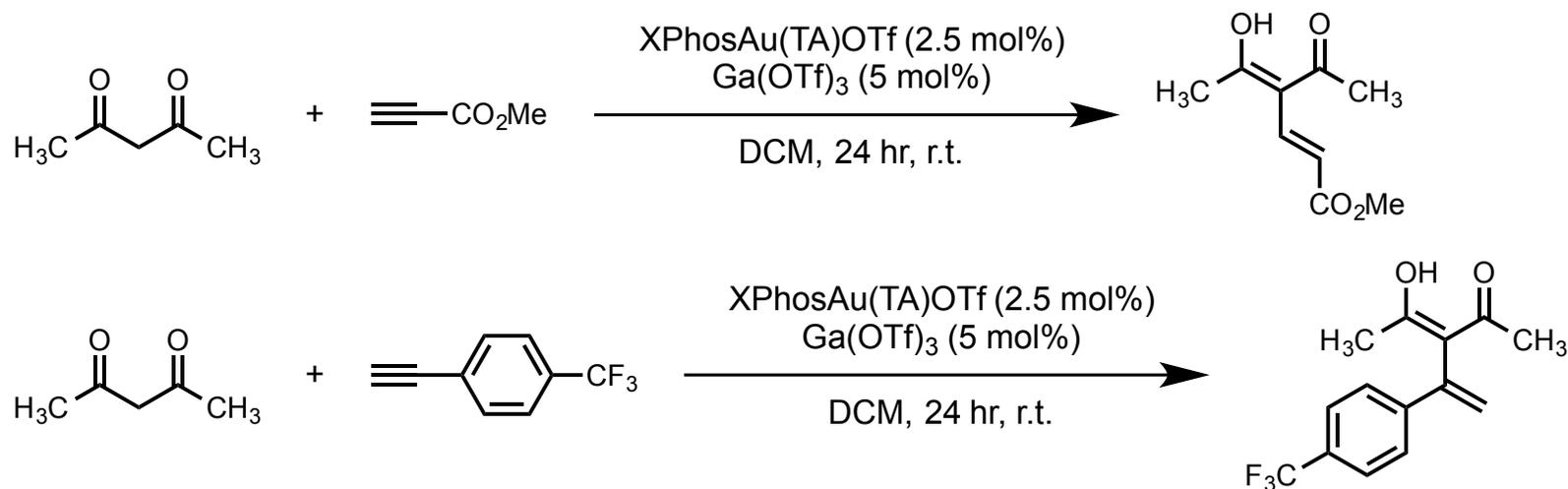
- Yields >80%, typically around 95%
- Tolerates R₁, R₂ = aryl, aliphatic, silyl

USE OF CATIONS OTHER THAN In(III): Au-Ga “SYNERGISTIC CATALYSIS”

- Reaction proceeds at room temperature
- Similar catalyst loadings (0.01-3 mol% Au, 5-10 mol% Ga)
- Requires both Au and Ga to proceed

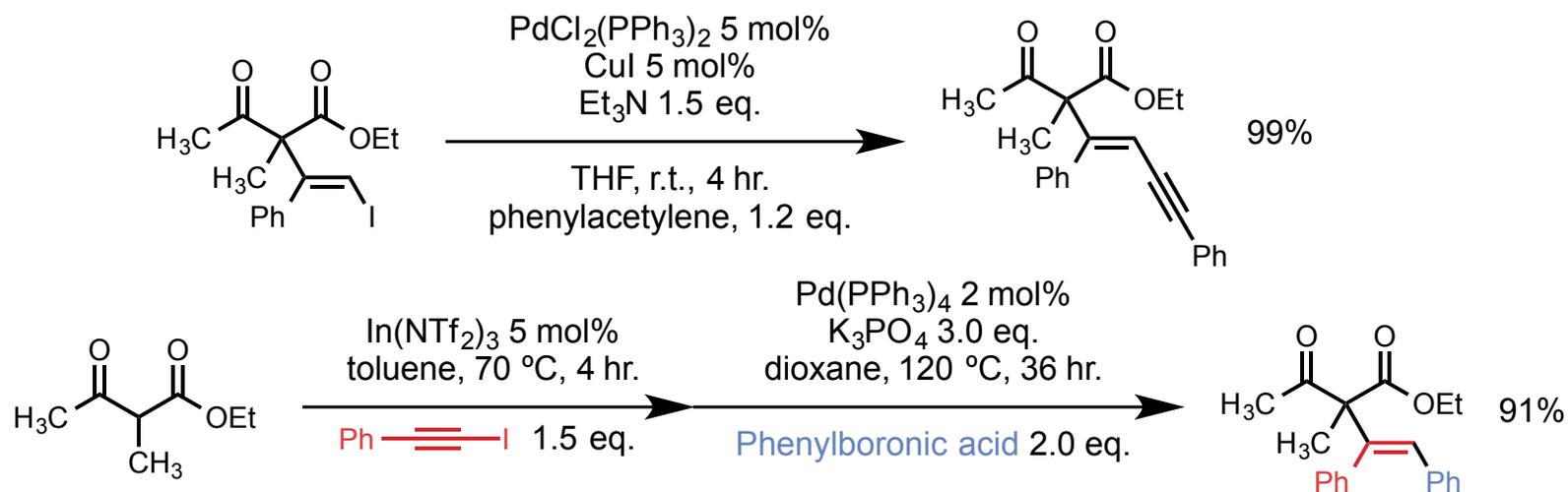


WHY THE SWITCH TO AN INTERNAL ALKENE?



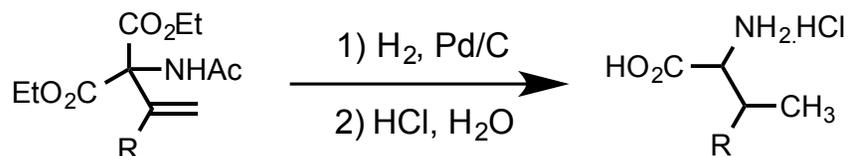
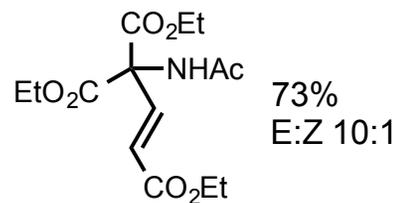
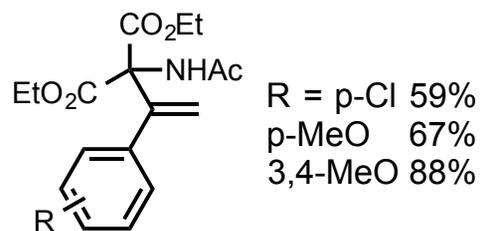
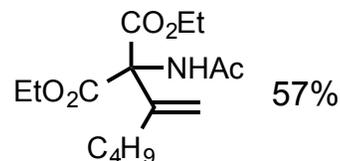
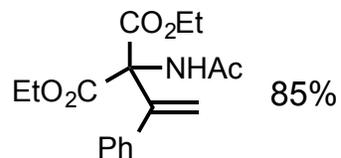
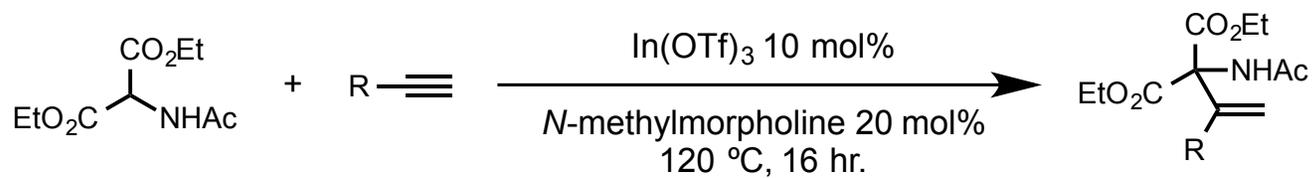
- The article gives no mention of the unusual switch in selectivity
- Possibly due to delocalization of the alkyne into the ester
- Could also be due to coordination by the ester to the Ga center

MODULAR SYNTHESIS: COUPLING TO IODIOALKENES

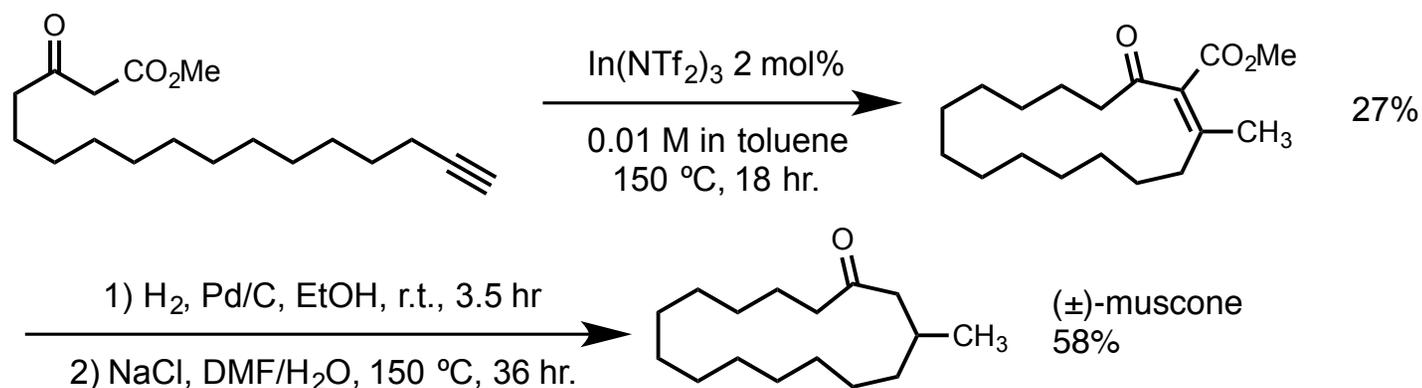


- ***E:Z* selectivity 100:0 (*Z* isomer not detected)**
- **$\text{In}(\text{NTf}_2)_3$ does not interfere with Suzuki coupling conditions—
one pot reactions work well**
- **Applies to the majority of dicarbonyl substrates previously mentioned, giving >80% yield in most cases**

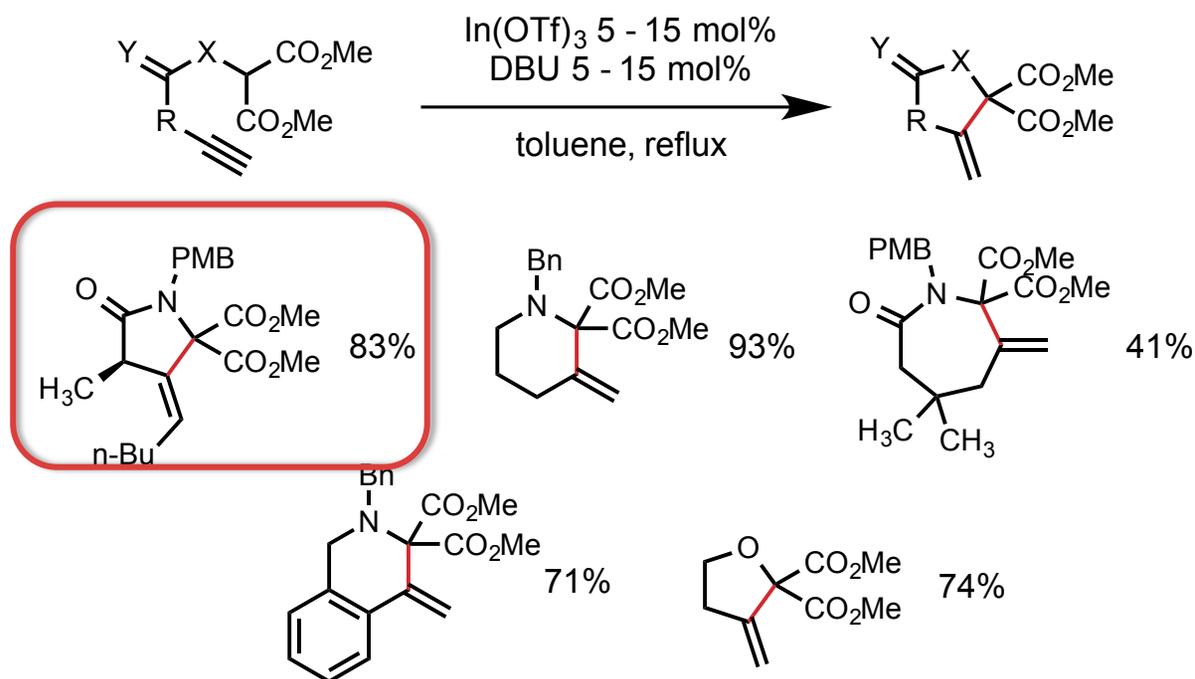
ADDITIONS TO ACETAMIDOMALONATE



NATURAL PRODUCT SYNTHESIS: THREE STEPS TO MUSCONE



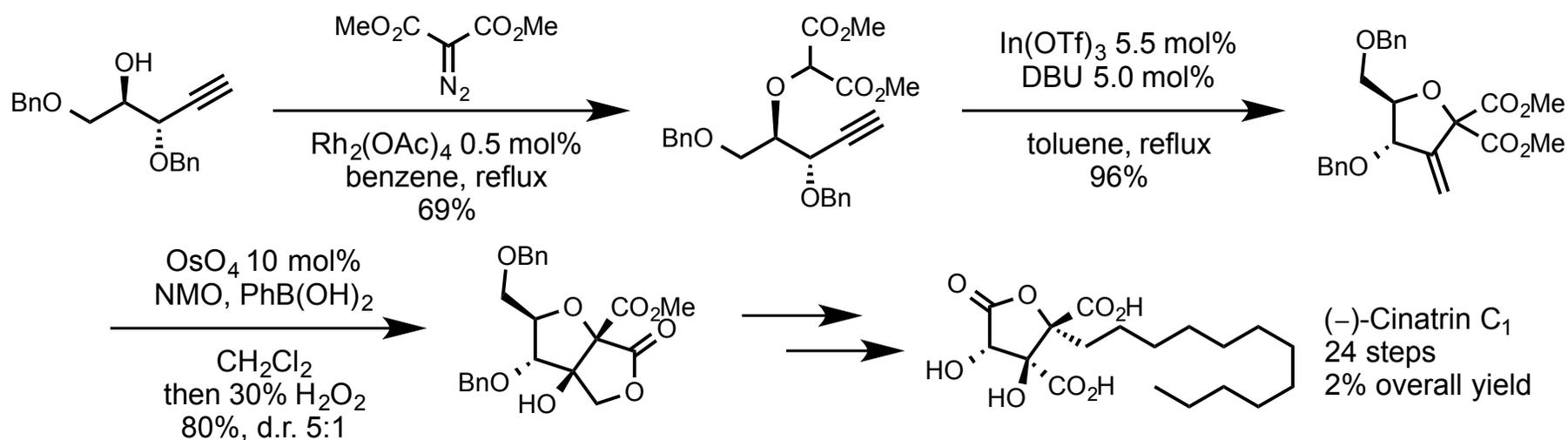
HETEROATOM-TETHERED MALONIC ESTERS



- Expands the scope of the intramolecular reaction
- Improves utility towards more complex natural product synthesis

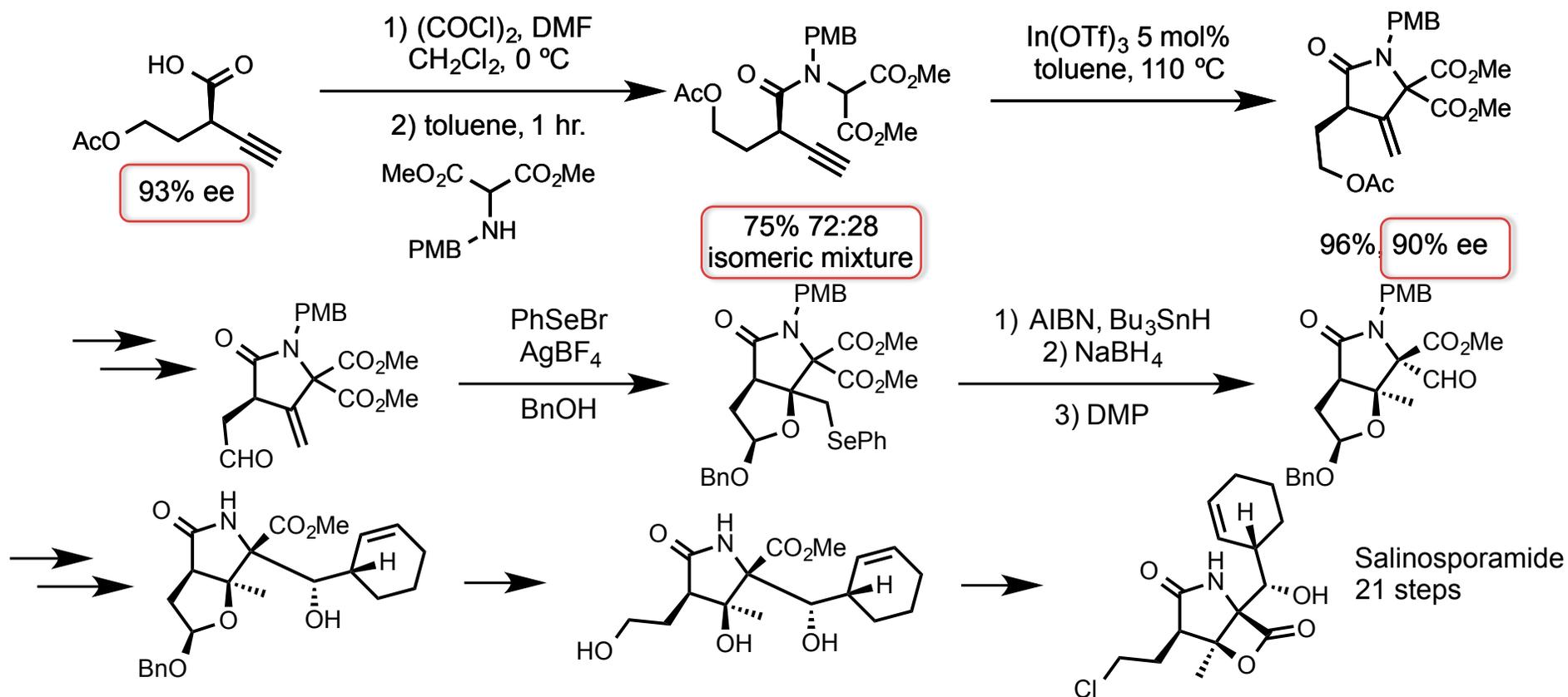
(a) Takahashi, K.; Midori, M.; Kawano, K.; Ishihara, J.; Hatakeyama, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 6244.
(b) Hatakeyama, S. *Pure Appl. Chem.* **2009**, *81*, 217.

NATURAL PRODUCT SYNTHESIS: EARLY-STAGE CYCLIZATION IN (-)-CINATRIN C₁



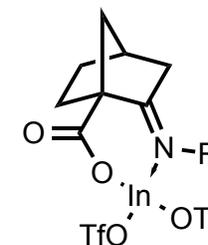
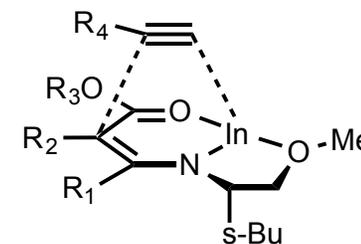
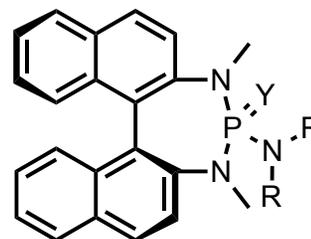
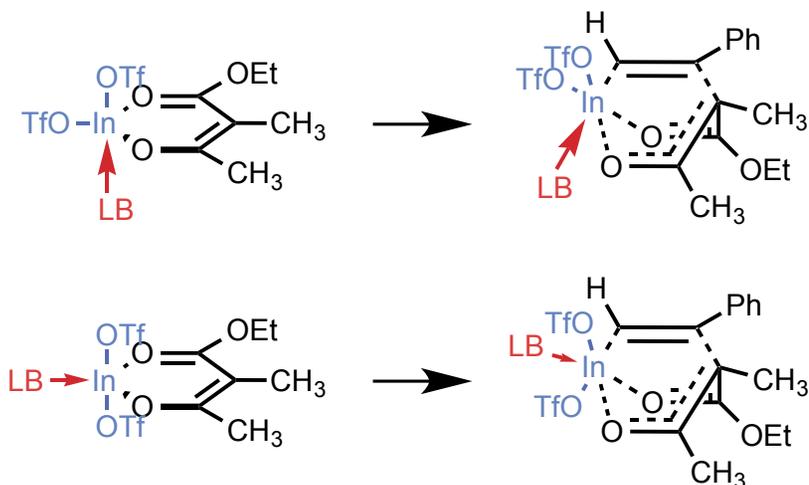
- Chosen as a cyclization method to selectively form *exo*-methylidenes and avoid alkene rearrangement into conjugation.

NATURAL PRODUCT SYNTHESIS: (-)-SALINOSPORAMIDE A



- The cyclization precursor underwent a spontaneous thermal conia-ene reaction, resulting in epimerization. In(OTf)₃ converted the rest of the material to the cyclized product with the expected retention of configuration.

FUTURE APPLICATIONS: LEWIS BASE CATALYSIS?



- **At present the reaction requires high temperatures in order to proceed to completion and in good yield**
- **Lewis base coordination could activate the indium enolate and increase reactivity**
- **Highly organized transition state could allow for asymmetric induction with a chiral Lewis base**
 - Has already proven successful with a “tethered” lewis basic chiral auxiliary

IMPORTANT RESOURCES

Seminal papers:

Nakamura, M.; Endo, K.; Nakamura, E. *J. Am. Chem. Soc.* **2003**, *125*, 13002.

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

OrgSyn:

Fujimoto, T.; Endo, K.; Nakamura, M.; Nakamura, E. *Org. Synth.* **2009**, *86*, 325.

Enantioselective:

Fujimoto, T.; Endo, K.; Tsuji, H.; Nakamura, M.; Nakamura, E. *J. Am. Chem. Soc.* **2008**, *130*, 4492.

Reviews:

Dénès, F.; Pérez-Luna, A.; Chemla, F. Addition of Metal Enolate Derivatives to Unactivated Carbon-Carbon Multiple Bonds. *Chem. Rev.* **2010**, *110*, 2366.

Dagorne, S.; Bellemin-Laponnaz, S. Group 13 Metal-Mediated Organic Reactions. *The Group 13 Metals Aluminium, Gallium, Indium and Thallium: Chemical Patterns and Peculiarities.* **2011**, 654.