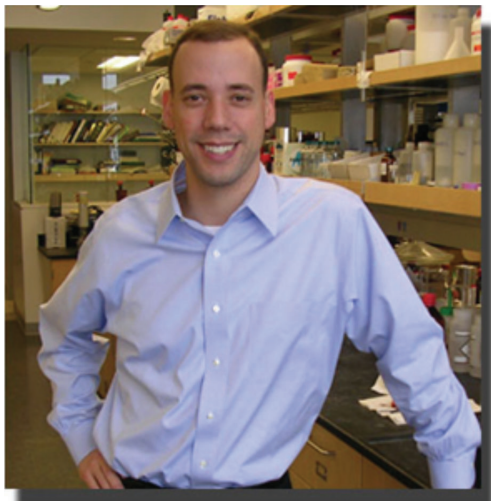


# Regioselective Reductive Cross-Coupling Reaction



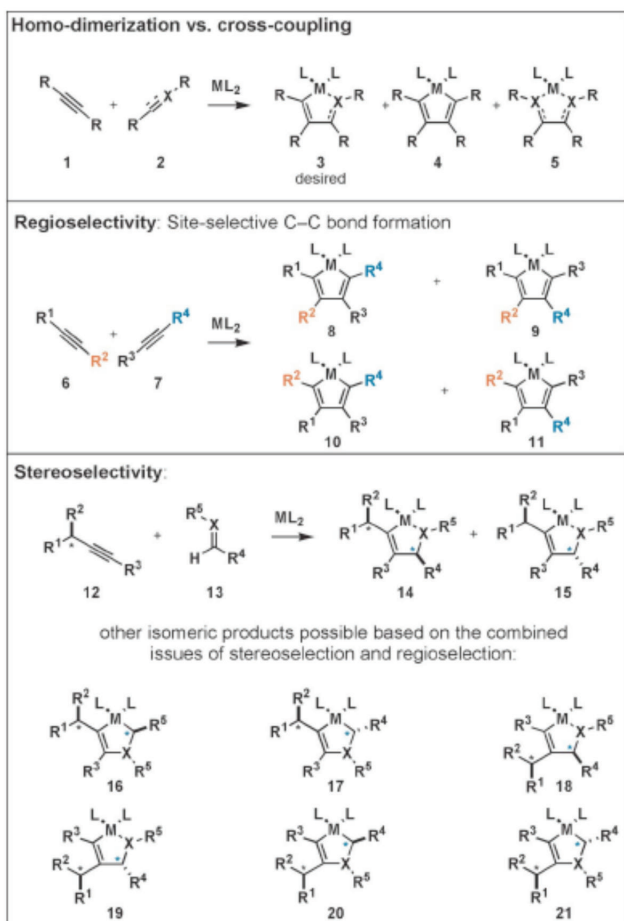
**Glenn C. Micalizio** obtained a Ph.D. at the University of Michigan in 2001 under the supervision of Professor William R. Roush. After postdoctoral study as a Fellow of the Helen Hay Whitney Foundation at Harvard University in the laboratory of Professor Stuart L. Schreiber, he moved to Yale University as an Assistant Professor in the Department of Chemistry (2003). In 2008, he moved to the Department of Chemistry at The Scripps Research Institute as an Associate Professor. His research is focused on the development of new synthetic methods and application of these methods to complex molecule synthesis.

recent review : G. C. Micalizio *et.al.* *Eur. J. Org. Chem.* **2010**, 391.

## Contents

0. Introduction (P. 1)
1. Micalizio work : Reductive Cross Coupling Reaction (P. 3)
  - 1.1. Alkyne with Alkyne (P. 3)
  - 1.2. Alkyne with Alkene (P. 5)
  - 1.3. Allene (P.7)
  - 1.4. Imine (P.9)
  - 1.5. Toward complex molecule (P. 10)
2. Mechanism of Ni-catalyzed reductive cross coupling reaction (P.13)
3. Summary and perspective (P.15)
4. Appendix (P.16)

## 0. Introduction

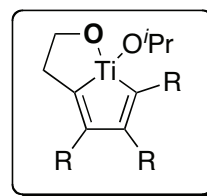


difficulty in control of reactivity and regioselectivity



## Micalizio's strategy

Ti-mediated alkoxide directed reductive cross coupling



[Ar]3d<sup>2</sup>4s<sup>2</sup>

- oxidation states : +4, +3 or +2
- coordination : 4-coordinated complex, 5 and 6
- bond energy : Ti-F > Ti-O > Ti-Cl > Ti-N > Ti-C (Ti-C < Zr-C)
- polarized Ti-C, cationic Ti
- reactivity of RTiL<sub>n</sub> is affected by the ligand at Ti

Yukikinzokuhannouzai -handbook , Kagakudouzin (P. 93)

## Why did Micalizio focus attention on Ti-mediated strategy?

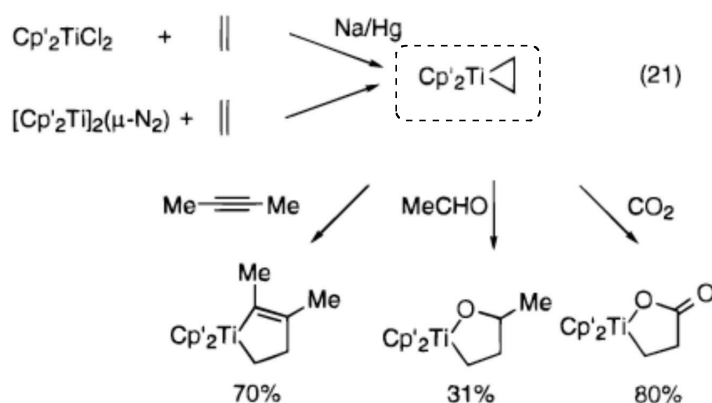
1. The ability of Ti alkoxide to undergo rapid and reversible ligand exchange.

### paste

mechanism of katsuki sharpless epoxidation in  
Strategic Applications of Named Reactions in Organic Chemistry (Kagakudouzin)

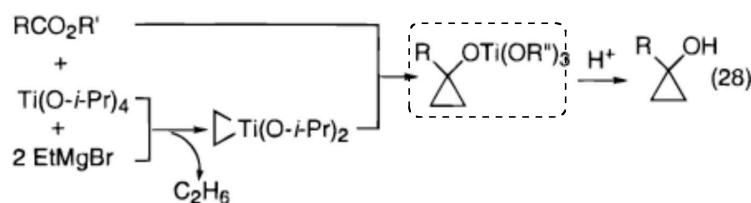
Sharpless et. al. *J. Am. Chem. Soc.* **1991**, *113*, 106.  
Katsuki T. et. al. *Org. React.* **1996**, *48*, 1.

2. Cp<sub>2</sub>Ti-π complex are known to participate reductive cross coupling.

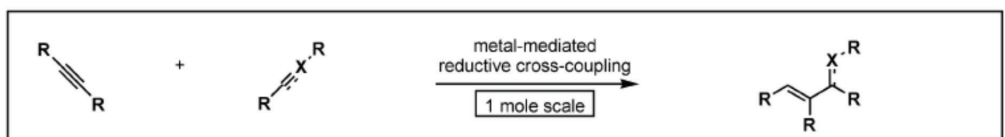


Bercaw et. al. *J. Am. Chem. Soc.* **1983**, *105*, 1136.  
Sato. et. al. *Chem. Rev.* **2000**, *100*, 2835

3. Ti alkoxide could be employed to access similar reactivity seen with Cp<sub>2</sub>Ti-π complexes (Kulinkovich, Sato)



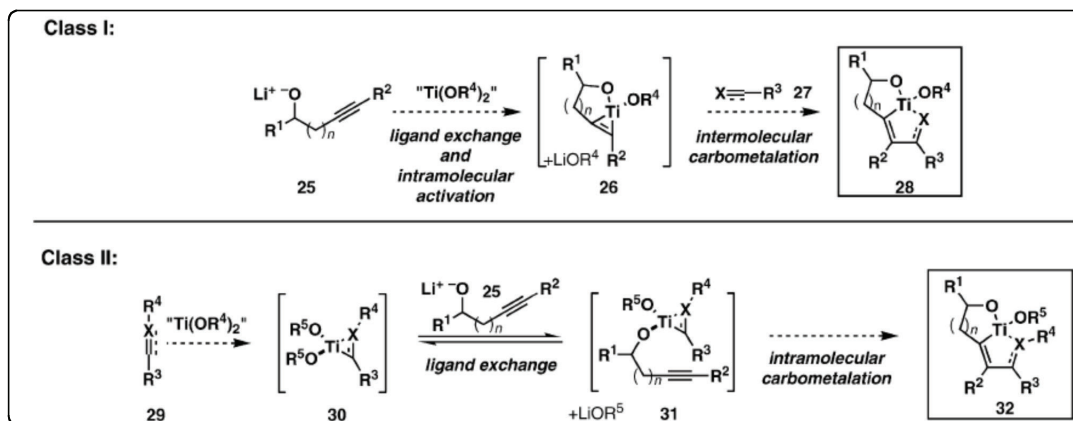
Kulinkovich et. al. *Zh. Org. Khim.* **1989**, *25*, 2244.



reagent	quantity required [a]	Cost [b] (Strem - 2008)	Cost [b] (Aldrich - 2009)
Stoichiometric Ti(O <i>i</i> Pr) <sub>4</sub> :	1 mol	\$18	\$18
10 mol-% Ni(COD) <sub>2</sub> :	0.1 mol	\$591	\$633
5 mol-% [Rh(COD) <sub>2</sub> ]OTf:	0.05 mol	\$4,391	\$3,337
5 mol-% [Ir(COD) <sub>2</sub> ]BARF:	0.05 mol	\$6,465	–
5 mol-% Ru(O <sub>2</sub> CCF <sub>3</sub> ) <sub>2</sub> (CO)(PPh <sub>3</sub> ) <sub>2</sub> :	0.05 mol	\$11,612	–

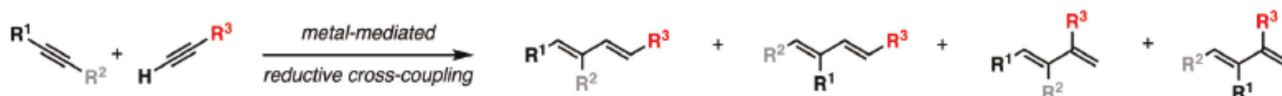
[a] Quantity is based on typical procedures reported in the literature for representative reductive cross-coupling reactions.  
[b] Cost depicted does not include additional required reagents. In the case of Ti-mediated processes, 2 equiv. of *i*PrMgCl is typically employed (cost on this scale is \$184). For the catalytic processes depicted, the cost of additional ligands is not included in this analysis.

the cost of stoichiometric Ti(O*i*Pr)<sub>4</sub> is significantly less than known catalytic systems based on Ni, Rh, Ir or Ru.



## Alkyne + Alkyne

Regiochemical possibilities in reductive cross-coupling:



Micalizio *et. al. J. Org. Chem.* **2009**, *74*, 7211.

### Class I

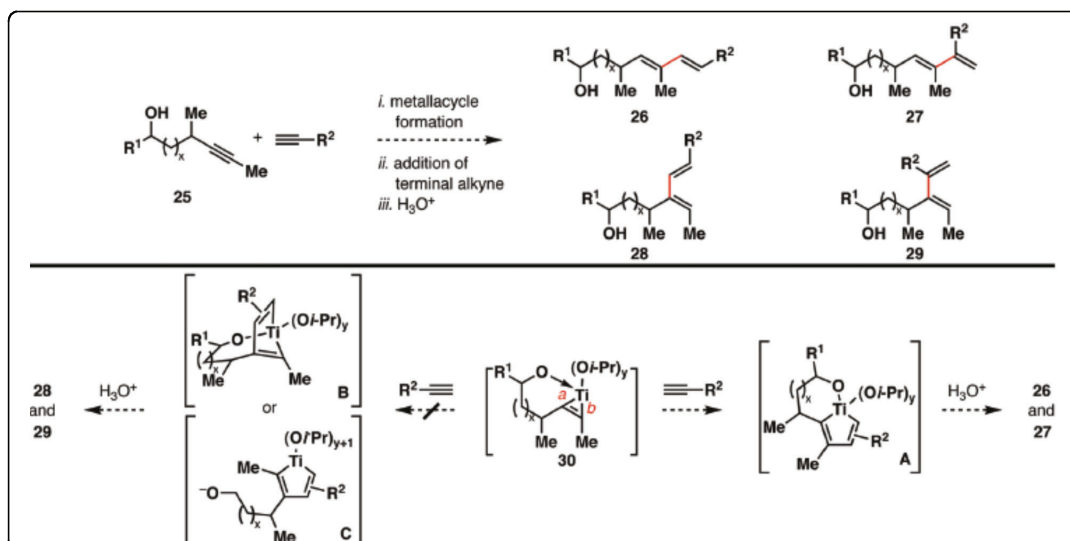
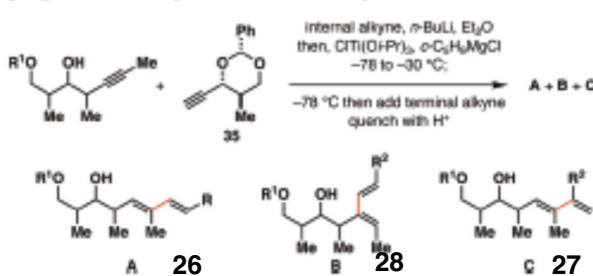
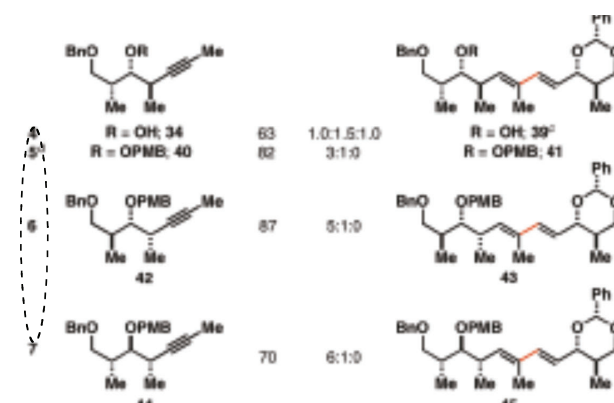


TABLE 1. Initial Study of Alkoxy-Directed Reductive Cross-Coupling of Internal Alkynes with Terminal Alkynes<sup>22</sup>

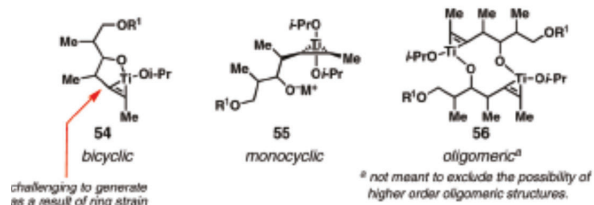


entry	internal alkyne	yield <sup>a</sup>	rr <sup>b</sup> (A:B:C)	major regioisomer
1		70	28:1:1	
2		50	15:2:1	
3		52	4:0:1	



<sup>a</sup>Yield based on terminal alkyne. <sup>b</sup>Regioisomeric ratio determined by <sup>1</sup>H NMR of the product mixture after flash column chromatography (see the Supporting Information for details). <sup>c</sup>Compound 39 is not the major isomer from this coupling reaction. <sup>d</sup>C(Ti)(O-Pr)<sub>3</sub>, o-C<sub>6</sub>H<sub>5</sub>MgCl, -78 to -30 °C, then -78 °C and addition of terminal alkyne.

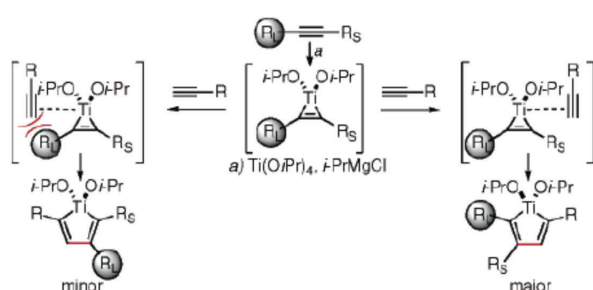
•O-protected alkyne gave products with moderate rr.



**FIGURE 9.** Uncertainty regarding the nature of the titanium-alkyne complex in the transition state for carbometalation and proposed perturbation.

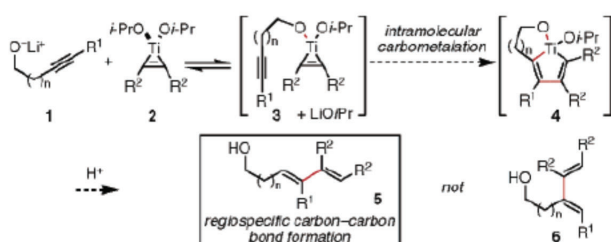
## Class II

Micalizio *et. al.* *J. Am. Chem. Soc.* **2006** *128*, 2764.

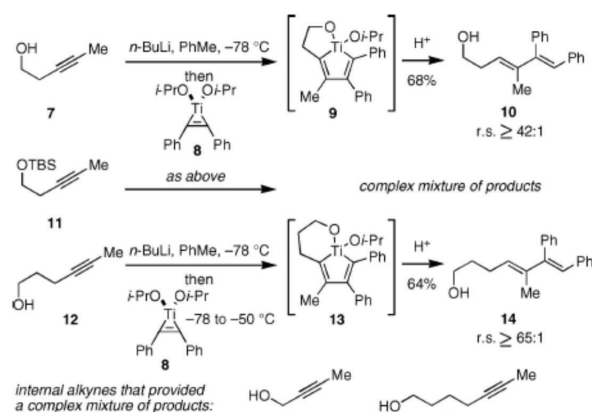


**Figure 1.** Background to the control of regioselection in group 4 metal-mediated coupling reactions of internal alkynes with terminal alkynes.

Substrate scope is limited based on factors influencing reactivity and regioselectivity.



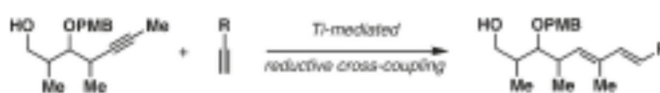
**Figure 2.** Directed carbometalation reaction for 1,3-diene synthesis.



**Figure 3.** Presence of the tethered alkoide and the length of the tether influence reactivity as well as regioselectivity.

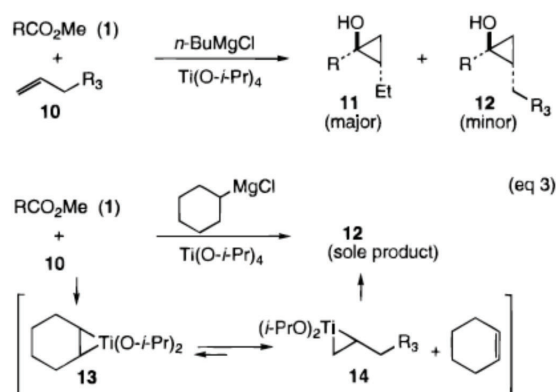
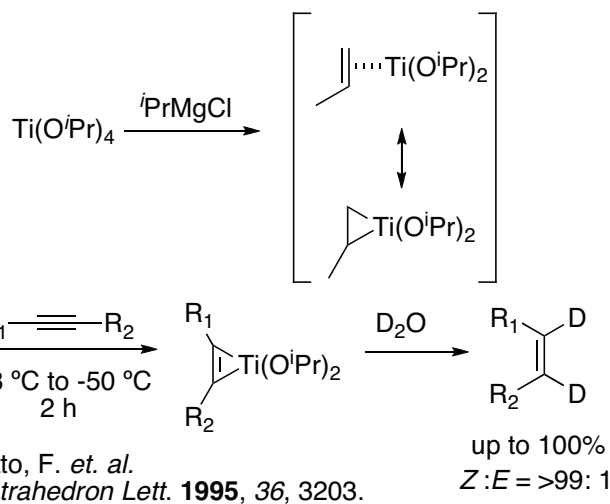
the tether alkoide plays a central role in determining regio selection.

**TABLE 2.** Highly Regioselective Alkoide-Directed Reductive Cross-Coupling Reactions of Internal Alkynes with Terminal Alkynes



entry	internal alkyne	terminal alkyne	yield <sup>a</sup>	r <sup>b</sup>	major regioisomer
1	60	35	60	17:1	64
2	61	35	57	$\geq 20:1$	65
3	62	35	47	$\geq 20:1$	66
4	72	35	53	$\geq 20:1$	73

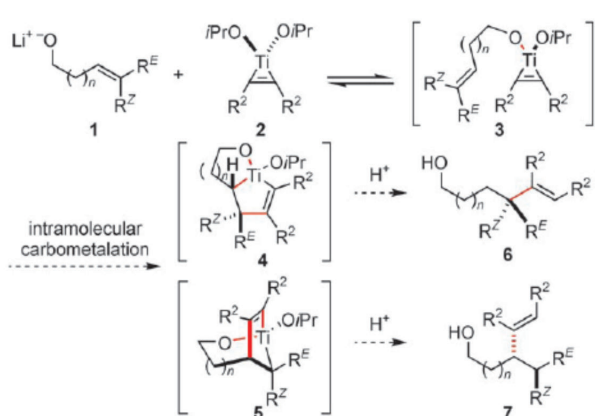
<sup>a</sup>Yield based on terminal alkyne. <sup>b</sup>Regioisomeric ratio with respect to functionalization of the internal alkyne (A/B) determined by <sup>1</sup>H NMR of the product mixture after a simple filtration column (see the Supporting Information for details). In a few cases, observable quantities of the minor regioisomer "C" (as defined in Table 1) were observed (entry 4 = 12:1, entry 6 = 14:1, entry 7 = 17:1).



Jin Kun Cha *et. al.* *J. Am. Chem. Soc.* **1996**, *118*, 4198.

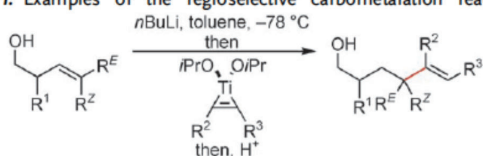
## 1.2 Alkyne with Alkene

Micalizio *et. al. Angew Chem.* **2007.** 119, 1462.

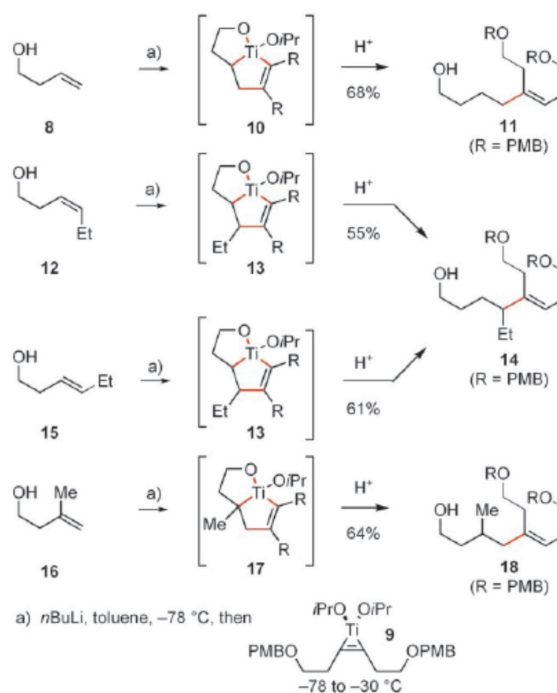


**Scheme 2.** A directed coupling of polysubstituted olefins and internal alkynes.

**Table 1:** Examples of the regioselective carbometalation reactions.



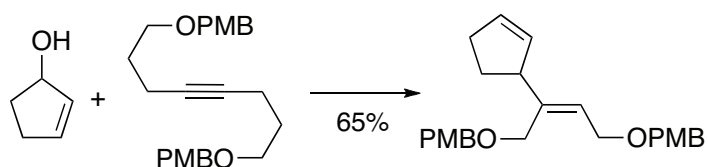
Entry	Unsaturated alcohol	First $\pi$ electrophile <sup>[a]</sup>	Yield [%]	Major regioisomer <sup>[b]</sup>
1			56	
2			50	
3			63	
4			58	
5			58	



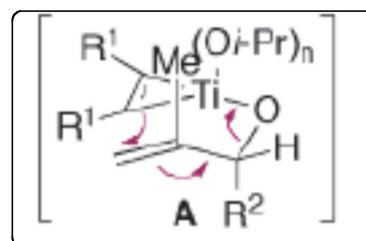
**Scheme 3.** Intermolecular alkoxy-directed coupling of substituted olefins and alkynes. PMB = *para*-methoxybenzyl.

Micalizio *et. al. J. Am. Chem. Soc.* **2007.** 129, 15112.

allylic alcohol case



alkyne (1.0 equiv),  $\text{CITi}(\text{O}i\text{-Pr})_3$ ,  $\text{PhMe}$ ,  $\text{C}_5\text{H}_9\text{MgCl}$ , -78 to -35 °C, then recool to -78 °C add Li-alkoxide of allylic alcohol (1.0 equiv) (-78 to 0 °C).



• via formal [3,3]-rearrangement route

<Blank Space>

### 1.3 Allen

#### 1.3.1 allene+ alkyne

Micalizio *et. al. Chem. Commun.* **2007**, 4531.

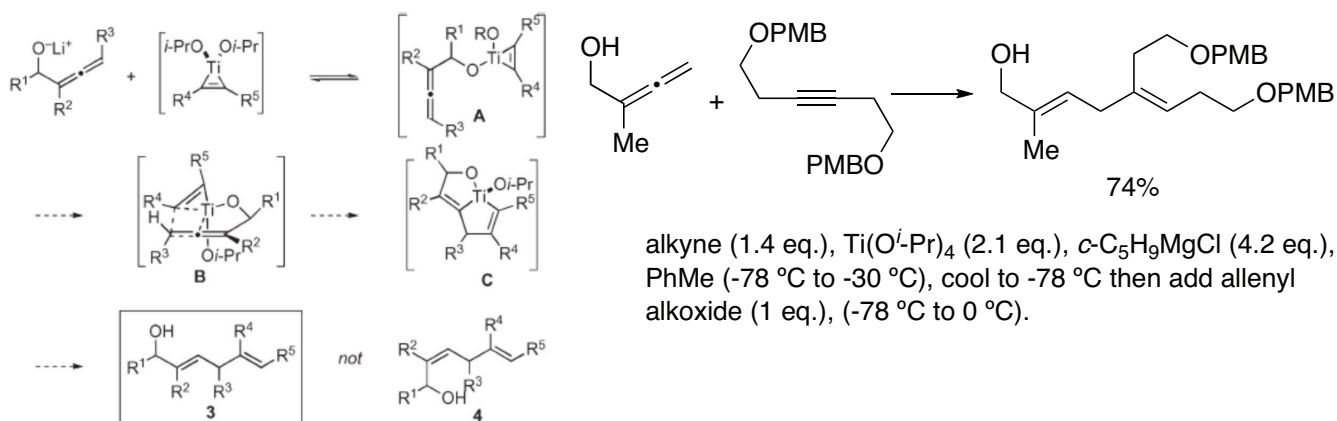
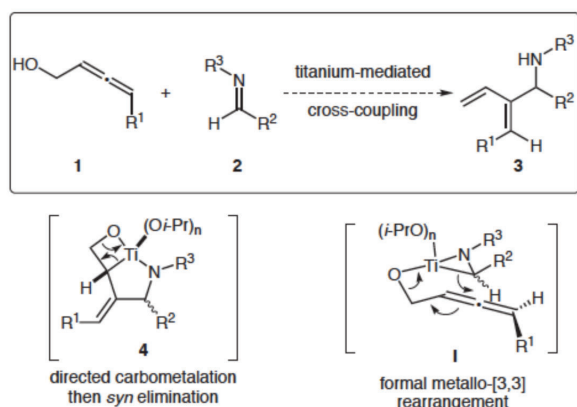
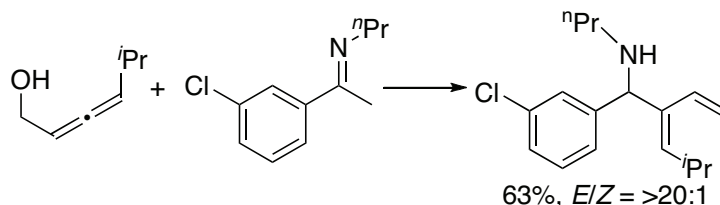


Fig. 2 Proposed pathway for site- and stereoselective bimolecular coupling of allenes and alkynes.

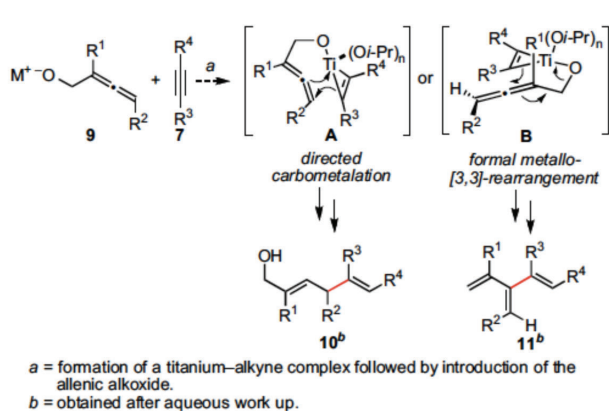


Scheme 2 Plan for allene-imine cross-coupling

#### 1.3.2 allene+ imine Micalizio *et. al. Synlett*, **2008**, 735.



Typical reaction conditions: imine (1.0 equiv), CITi(Oi-Pr)<sub>3</sub> (1.25 equiv), *c*-C<sub>5</sub>H<sub>9</sub>MgCl (2.5 equiv), Et<sub>2</sub>O (-78 °C to -40 °C), then add allenyl alkoxide (3-4 equiv, -40 °C to 0 °C).



Scheme 3. A titanium-mediated, alkoxide-directed allene-alkyne cross-coupling.

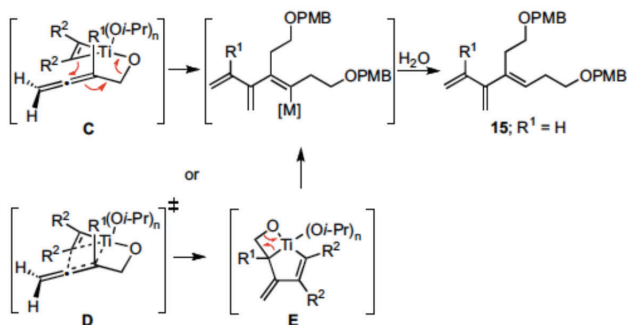
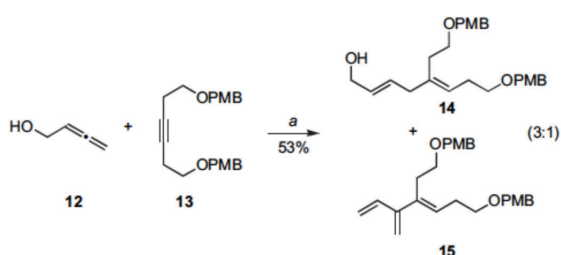


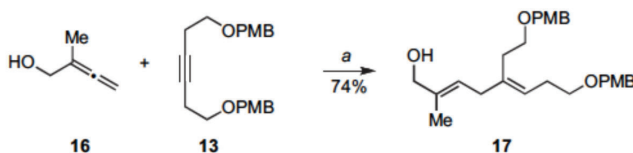
Figure 1. Possible origins of the cross-conjugated triene product 15.

Micalizio *et. al. Tetrahedron* **2008**, *68*, 3437.



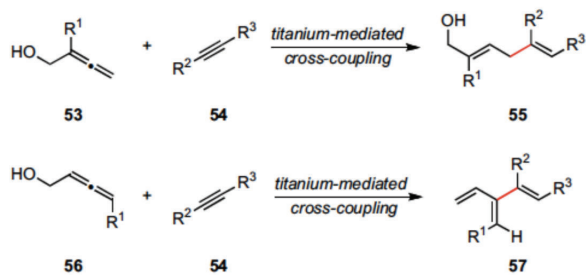
a = alkyne (1.0 equiv), CITi(Oi-Pr)<sub>3</sub> (2.0 equiv), *c*-C<sub>5</sub>H<sub>9</sub>MgCl (4.0 equiv), PhMe (-78 to -30 °C), cool to -78 °C, then add lithium alkoxide of allene (0.7 equiv) (-78 to 0 °C).

Scheme 4. A stereodefined 1,4-diene and cross-conjugated triene from an alkoxide-directed allene-alkyne coupling.



a = alkyne (1.4 equiv), CITi(Oi-Pr)<sub>3</sub> (2.1 equiv), *c*-C<sub>5</sub>H<sub>9</sub>MgCl (4.3 equiv), PhMe (-78 to -30 °C), cool to -78 °C, then add lithium alkoxide of allene (1 equiv) (-78 to 0 °C).

Scheme 5. Cross-coupling of 1,1-disubstituted allenes with internal alkynes proceeds with high levels of site-selectivity.



Scheme 12. Allene-alkyne cross-coupling for the synthesis of 1,4-dienes or cross-conjugated trienes.

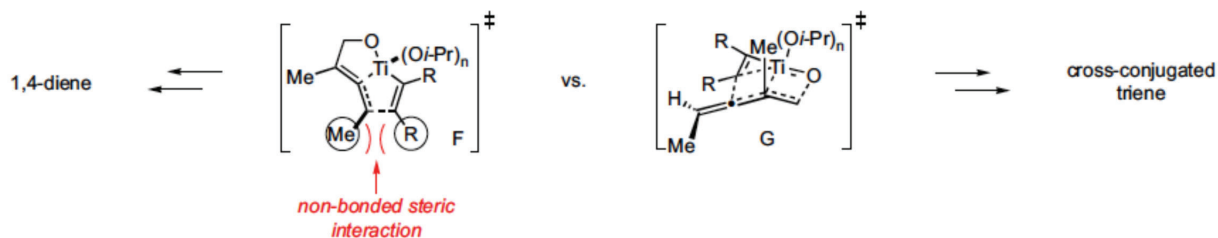
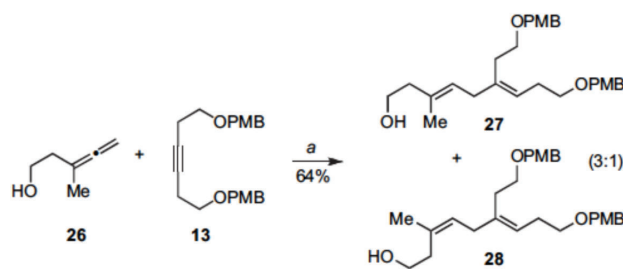


Figure 3. Competition between directed carbometalation and formal metallo-[3,3] rearrangement with trisubstituted allenes.



*a* = alkyne (1.4 equiv),  $\text{CITi}(\text{O}i\text{-Pr})_3$  (2.1 equiv),  $c\text{-C}_6\text{H}_9\text{MgCl}$  (4.2 equiv), PhMe ( $-78$  to  $-30$  °C), cool to  $-78$  °C, then add lithium alkoxide of allene (1 equiv) ( $-78$  to  $0$  °C).

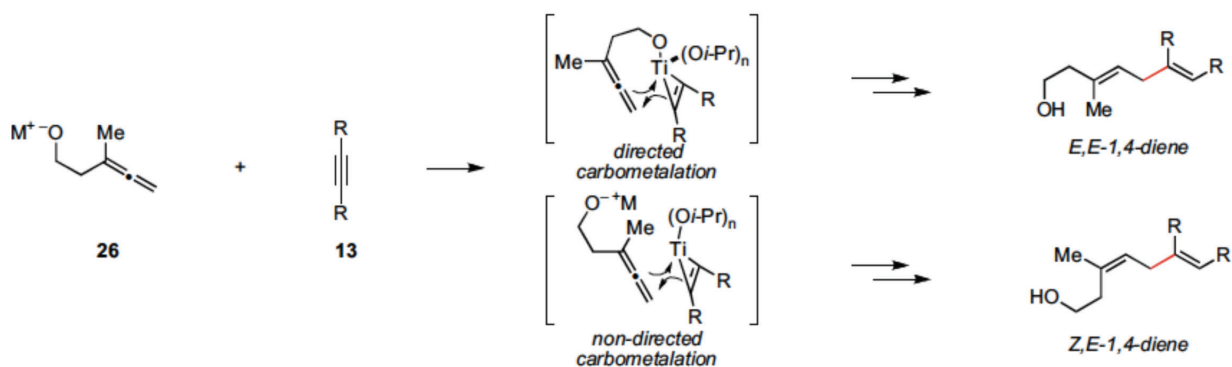


Figure 2. Competition between directed and non-directed carbometalation.



## 1.4. Imine

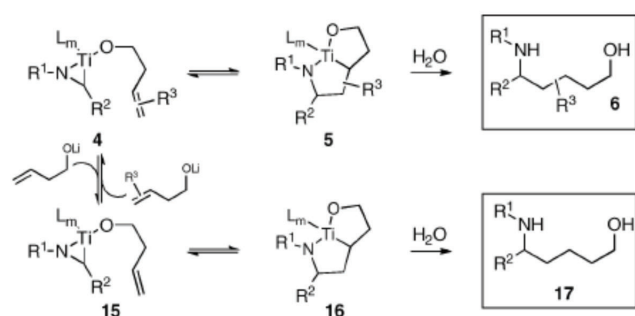
(Micalizio et.al. *Angew. Chem. Int. Ed.* **2007**, *46*, 391.)

**Table 1:** Stereoselective synthesis of unsaturated 1,5-amino alcohols.<sup>[a]</sup>

Entry	Imine	Unsaturated alkoxyde	Yield [%]	Major regioisomer
1	<b>7</b>	<b>8</b>	65	<b>9</b>
2	<b>7</b>	<b>10</b> : R = Et	60	<b>11</b> : R = Et
3	<b>7</b>	<b>12</b> : R = <i>i</i> Pr	53	<b>13</b> : R = <i>i</i> Pr
4	<b>7</b>	<b>14</b> : R = TMS	55	<b>15</b> : R = TMS

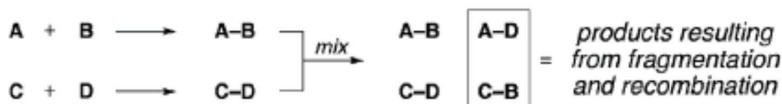
[a] Reaction conditions: Ti(O*i*Pr)<sub>4</sub>, *c*-C<sub>5</sub>H<sub>9</sub>MgCl, Et<sub>2</sub>O, -78 to -40 °C, then unsaturated alkoxyde (-40 to 0 °C), quenched with sat. aq NH<sub>4</sub>Cl. TMS = trimethylsilyl.

(Micalizio et.al. *Chem Commun.* **2010**, *46*, 3336.)

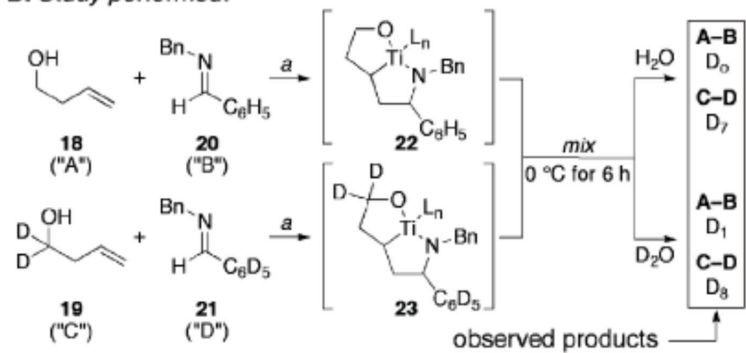


**Fig. 4** Potential equilibria for alkene exchange.

### A. General reaction scheme:



### B. Study performed:



<sup>a</sup> Reaction conditions: Imine (1 equiv), Ti(O*i*Pr)<sub>4</sub>, *c*-C<sub>5</sub>H<sub>9</sub>MgCl, Et<sub>2</sub>O (-78 to -40 °C), then add Li-alkoxyde of homoallylic alcohol (1.5 equiv) (-40 to 0 °C).

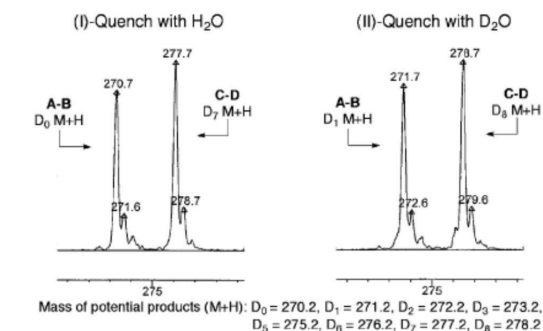
aza-Pauson Khand-like annulation reaction for the synthesis of tetrasubstituted  $\gamma$ -lactams

**Table 2:** Stereoselective synthesis of tetrasubstituted  $\alpha,\beta$ -unsaturated  $\gamma$ -lactams.<sup>[a]</sup>

Entry	Imine	Unsaturated alkoxyde	Yield [%]	Major regioisomer
1	<b>16</b>	<b>8</b> ; R = Me	66	<b>17</b> ; R = Me
2	<b>16</b>	<b>10</b> ; R = Et	61	<b>18</b> ; R = Et
3	<b>16</b>	<b>12</b> ; R = <i>i</i> Pr	64	<b>19</b> ; R = <i>i</i> Pr
4	<b>16</b>	<b>14</b>	49	<b>20</b>
5	<b>21</b>	<b>8</b>	55	<b>22</b> d.r. = 4:1
6	<b>23</b>	<b>12</b>	63	<b>24</b>
7	<b>25</b>	<b>10</b>	59	<b>26</b>

[a] Reaction conditions: Ti(O*i*Pr)<sub>4</sub>, *c*-C<sub>5</sub>H<sub>9</sub>MgCl, PhMe, -78 to -30 °C, then unsaturated alkoxyde (-30 to 0 °C), then CO<sub>2</sub> (20 psi) 90 °C, 48 h. Bn = benzyl.

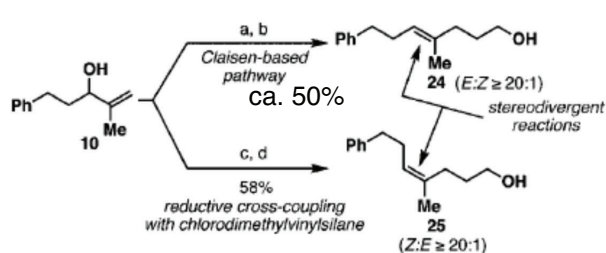
### C. LRMS of crude reaction mixture:



carbometalation process is irreversible.

## Toward complex molecule

Micalizio et. al. *J. Am. Chem. Soc.* **2008**, *130*, 16870



**Figure 5.** A stereochemically complementary process with respect to the Claisen rearrangement. Reaction conditions: (a) Johnson *o*-ester Claisen rearrangement; (b) reduction;<sup>9</sup> (c) 20,  $\text{CITi}(\text{O}i\text{-Pr})_3$ ,  $c\text{-C}_5\text{H}_9\text{MgCl}$ ,  $\text{Et}_2\text{O}$  ( $-78$  to  $-50$  °C), then cool to  $-78$  °C and add lithium alkoxide of 10 ( $-78$  to  $0$  °C) then,  $\text{HCl}$  (1 N) (75%,  $Z/E \geq 20:1$ ); (d) *t*-BuOOH,  $\text{CsOH} \cdot \text{H}_2\text{O}$ , TBAF, DMF,  $70$  °C.

a)  $\text{MeC}(\text{MgBr})\text{CH}_2$ ,  $\text{MeC}(\text{OMe})_3$ ,  $\text{EtCOOH}$  (cat), reflux

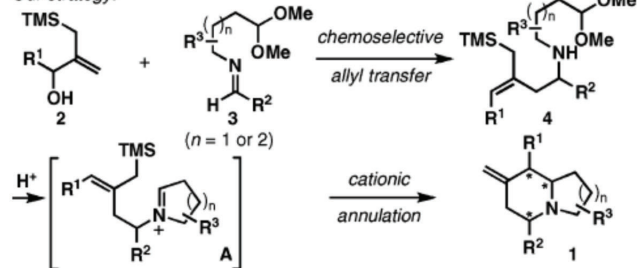
**Table 1**

entry	allylic alcohol	vinylsilane	yield (%)	( <i>Z</i> : <i>E</i> )	dr	product
1 <sup>a</sup>		2	62	≥ 20:1	-	
2 <sup>a</sup>		2	71	≥ 20:1	-	

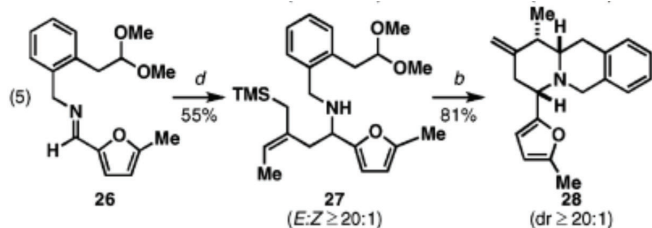
Reaction conditions: (a) *n*-BuLi (1 equiv), vinylsilane (3 equiv),  $\text{CITi}(\text{O}i\text{-Pr})_3$  (3 equiv),  $c\text{-C}_5\text{H}_9\text{MgCl}$  (6 equiv) ( $-78$  to  $0$  °C), then  $\text{HCl}$  (1 N); (b) *n*-BuLi (2 equiv), vinylsilane (3 equiv),  $\text{CITi}(\text{O}i\text{-Pr})_3$  (3 equiv),  $c\text{-C}_5\text{H}_9\text{MgCl}$  (6 equiv) ( $-78$  to  $0$  °C), then  $\text{HCl}$  (1 N).

(Micalizio et. al. *J. Am. Chem. Soc.* **2009**, *48*, 3648.)

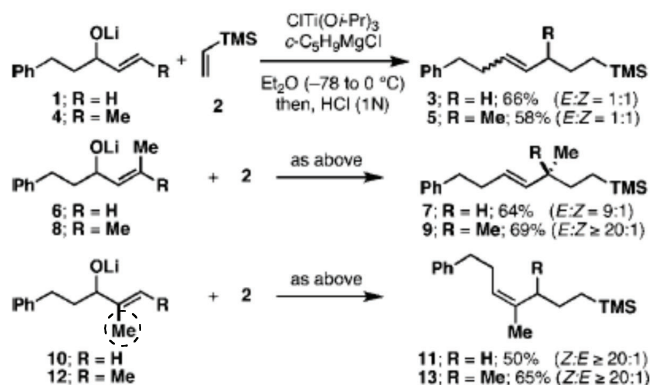
Our strategy:



**Figure 2.** Indolizidine and quinolizidine synthesis via (top) chemoselective allyl transfer followed by (bottom) cationic annulation.



(d) Imine (2.0 equiv),  $\text{Ti}(\text{O}i\text{-Pr})_4$  (3.0 equiv),  $c\text{-C}_5\text{H}_9\text{MgCl}$  (6.0 equiv), **8** (1 equiv),  $\text{Et}_2\text{O}$ .  
(b)  $\text{HCl}(\text{aq})$ , THF.



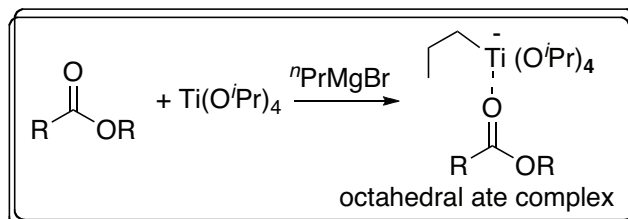
**Figure 3.** Preliminary study of stereoselection in reductive cross-coupling of allylic alcohols with vinylsilanes.

control by minimization of A-1,2 strain:



• This empirical model does not yet address the number of ligands present on the metal center in the transition state.

• Others have suggested **ate complexes** as reactive intermediates in the Kulinkovich reaction.

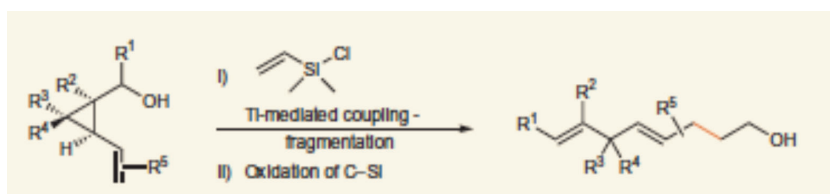
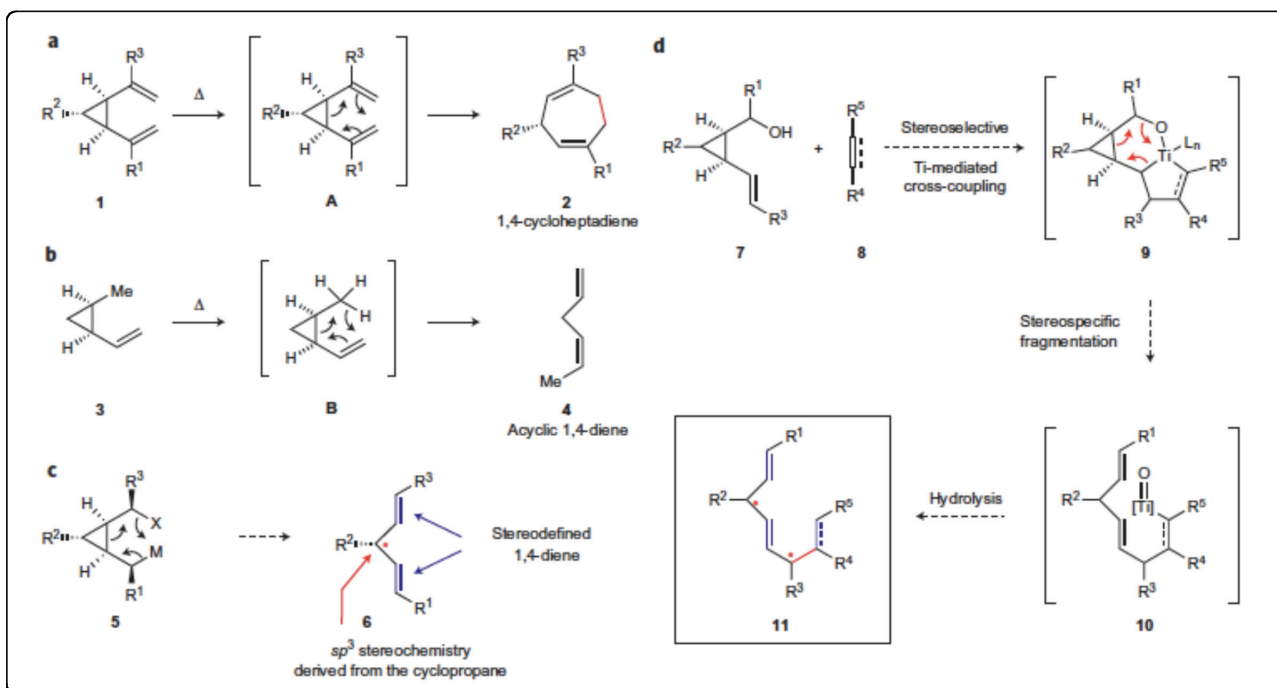


Kulinkovich et. al. *Eur. J. Org. Chem.* **2007**, 2121.

**Table 1.** Initial Exploration of the Chemoselective Coupling Reaction

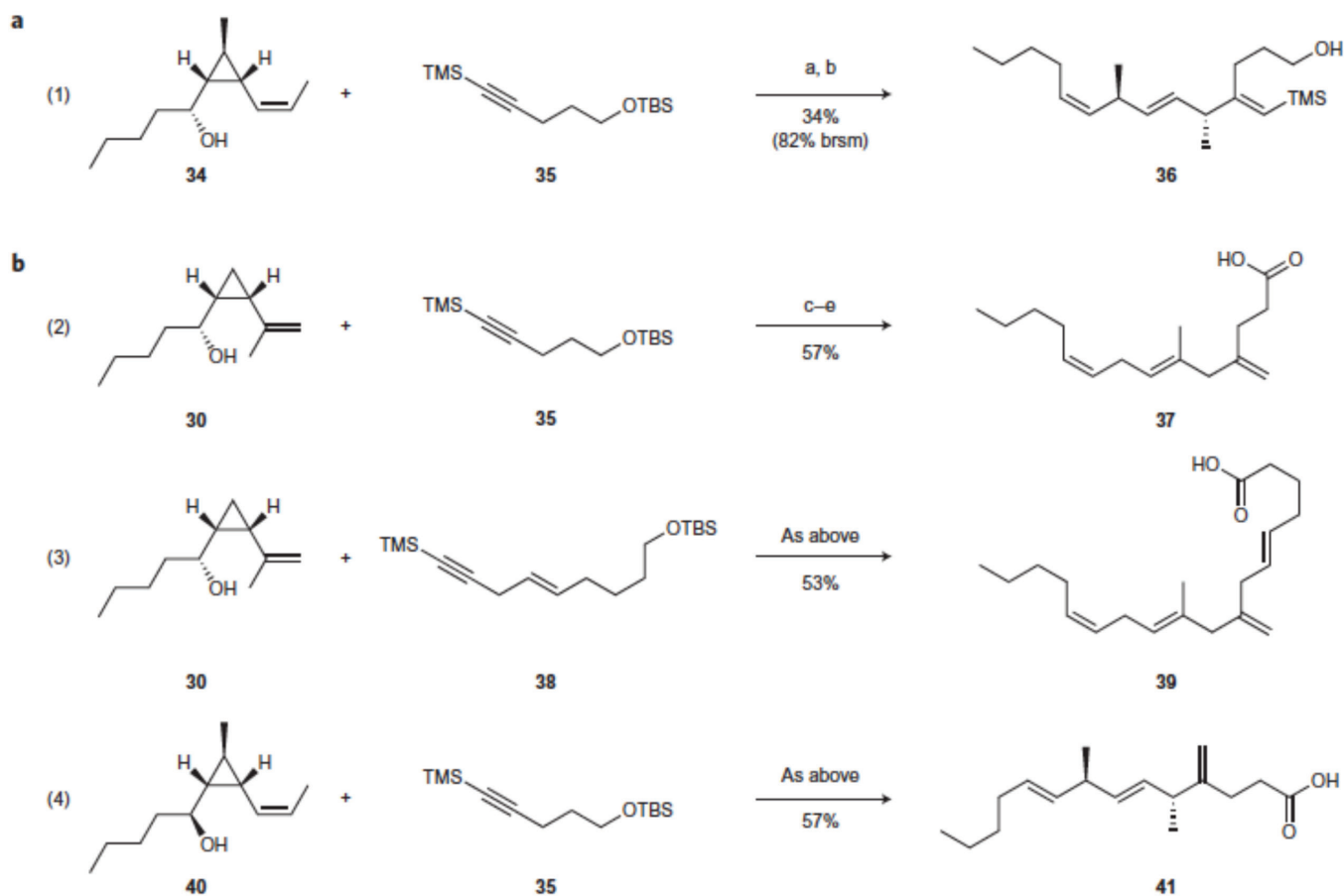
entry	allylic silane	yield (%)	<i>E</i> : <i>Z</i>	dr	major product <sup>a</sup>
1		75	-	-	
2		70	20:1	-	
3		70	-	-	
4		51	20:1	20:1	

<sup>a</sup> Reaction conditions: **5** (1 equiv),  $\text{Ti}(\text{O}i\text{-Pr})_4$  (1.5 equiv),  $c\text{-C}_5\text{H}_9\text{MgCl}$  (3.0 equiv), allylic alkoxide (1.5 equiv),  $\text{Et}_2\text{O}$ ,  $-78$  °C to rt. <sup>b</sup> The desired homoallylic amine product was isolated in 18% yield. <sup>c</sup> The relative stereochemistry of **13** was assigned by analogy to previous examples.<sup>8</sup>



Vinylcyclopropane	Presumed metallacyclic intermediate*	Yield (%) <sup>†</sup>	(E:Z) <sup>‡</sup>	dr <sup>‡</sup>	Product <sup>§</sup>
		58 (82% brsm)	20:1	-	
		54	20:1	-	
		50	20:1	-	
		61	10:1	-	
		55	20:1	20:1	

- 1) Reaction conditions for cross-coupling: vinylsilane,  $\text{CITi}(\text{Oi-Pr})_3$ ,  $\text{c-C}_5\text{H}_9\text{MgCl}$ ,  $\text{Et}_2\text{O}$  (-78 to -50 °C), then add lithium alkoxide of vinylcyclopropane (-70 °C to room temperature over 3 h). Oxidation conditions: TBHP,  $\text{H}_2\text{O}$ ,  $\text{CsOH}\cdot\text{H}_2\text{O}$ , TBAF, DMF, 70 °C.
- 2) Oxidation conditions: KF,  $\text{KHCO}_3$ ,  $\text{H}_2\text{O}_2$ , MeOH, THF.  $\text{CH}_2\text{Cl}_2$ ,  $\text{Sm}[\text{Hg}]$ , THF, (85%, dr = 20:1). PDC, 4-Å molecular sieves,  $\text{CH}_2\text{Cl}_2$  (91%), then L-Selectride, THF (76% of desired isomer, dr = 6:1).



(a)  $\text{CITi}(\text{O}i\text{-Pr})_3$ ,  $c\text{-C}_5\text{H}_9\text{MgCl}$ , **35** (-78 to 30 °C), PhMe, then lithium alkoxide of **34** in  $\text{Et}_2\text{O}$  (-70 °C to room temperature over 3 h)

(b) TBAF, THF

(c)  $\text{CITi}(\text{O}i\text{-Pr})_3$ ,  $c\text{-C}_5\text{H}_9\text{MgCl}$ , alkyne (-78 to -30 °C), PhMe, then lithium alkoxide of the vinylcyclopropane in  $\text{Et}_2\text{O}$  (-70 °C to room temperature over 3 h);

(d) HF.pyr,  $\text{CH}_3\text{CN}$ ,  $\text{CH}_2\text{Cl}_2$ ;

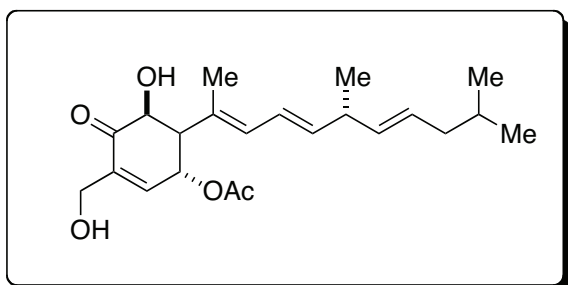
(e) PDC, DMF,  $\text{H}_2\text{O}$ .

Yields reported are over the three-step sequence (c-e) and are adjusted based on the quantity of recovered starting material (vinylcyclopropane). Isolated yields for each reaction sequence are 38% (equation (2)), 36% (equation (3)) and 23% (equation (4)) over the three-step process (corresponding to average yields of 60-70% per step).

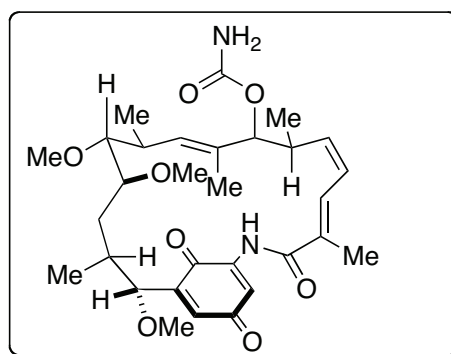
### total synthesis

Micalizio *et. al.* *J. Am. Chem. Soc.* **2009**, 131, 1392.

Micalizio *et. al.* *Angew. Chem. Int. Ed.* **2008**, 47, 4005.

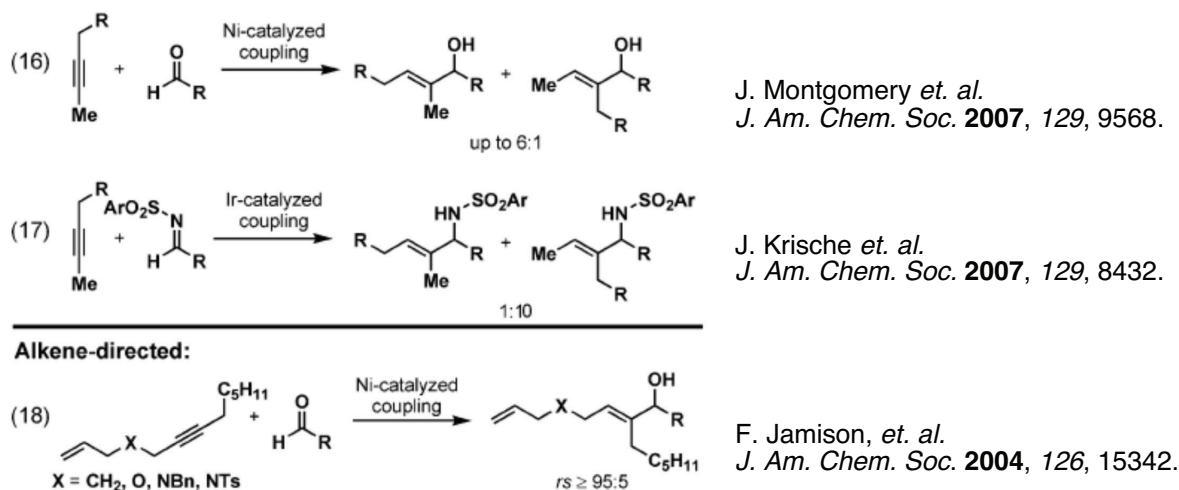


**Phorbacin C**



**Macbecin I**

## 2. Mechanism of Ni-catalyzed reductive cross coupling reaction

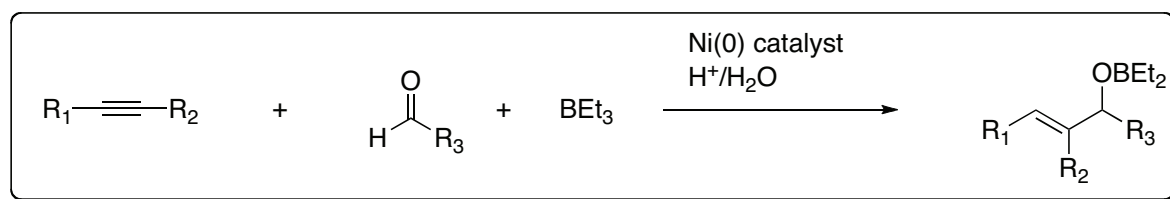


J. Montgomery *et. al.*  
*J. Am. Chem. Soc.* **2007**, *129*, 9568.

J. Krische *et. al.*  
*J. Am. Chem. Soc.* **2007**, *129*, 8432.

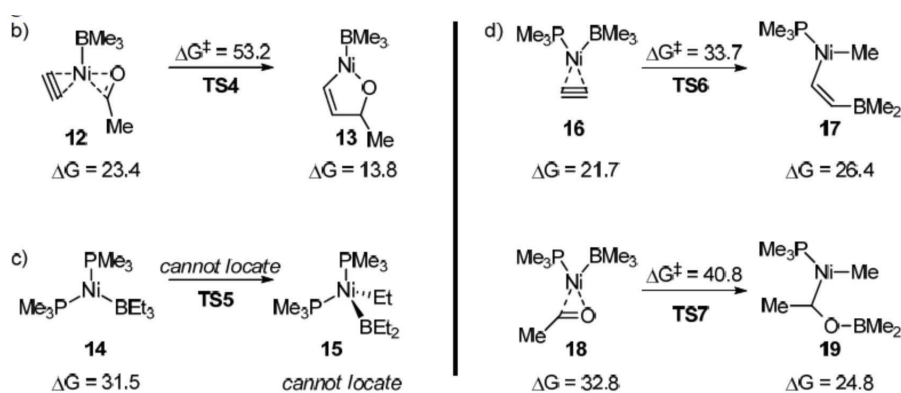
F. Jamison, *et. al.*  
*J. Am. Chem. Soc.* **2004**, *126*, 15342.

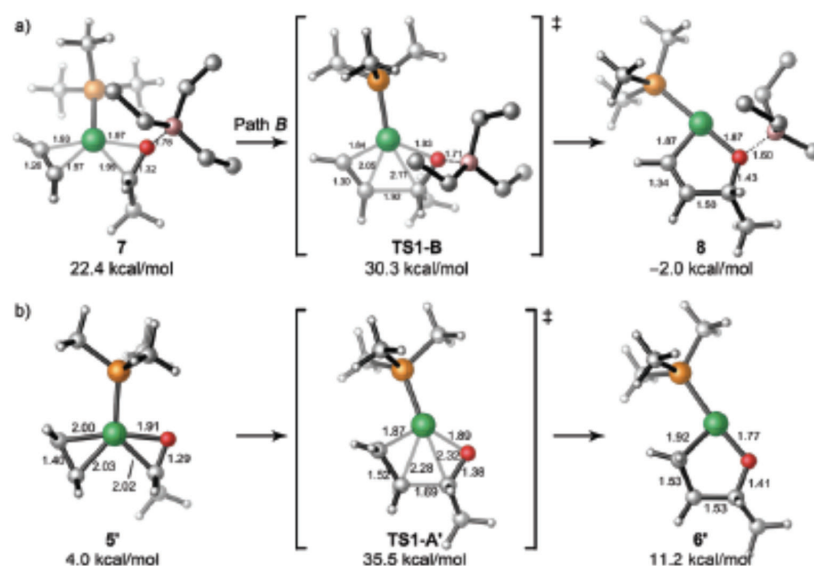
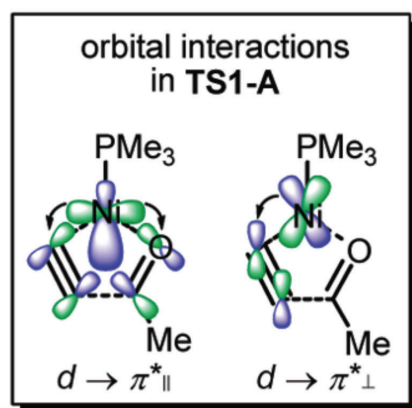
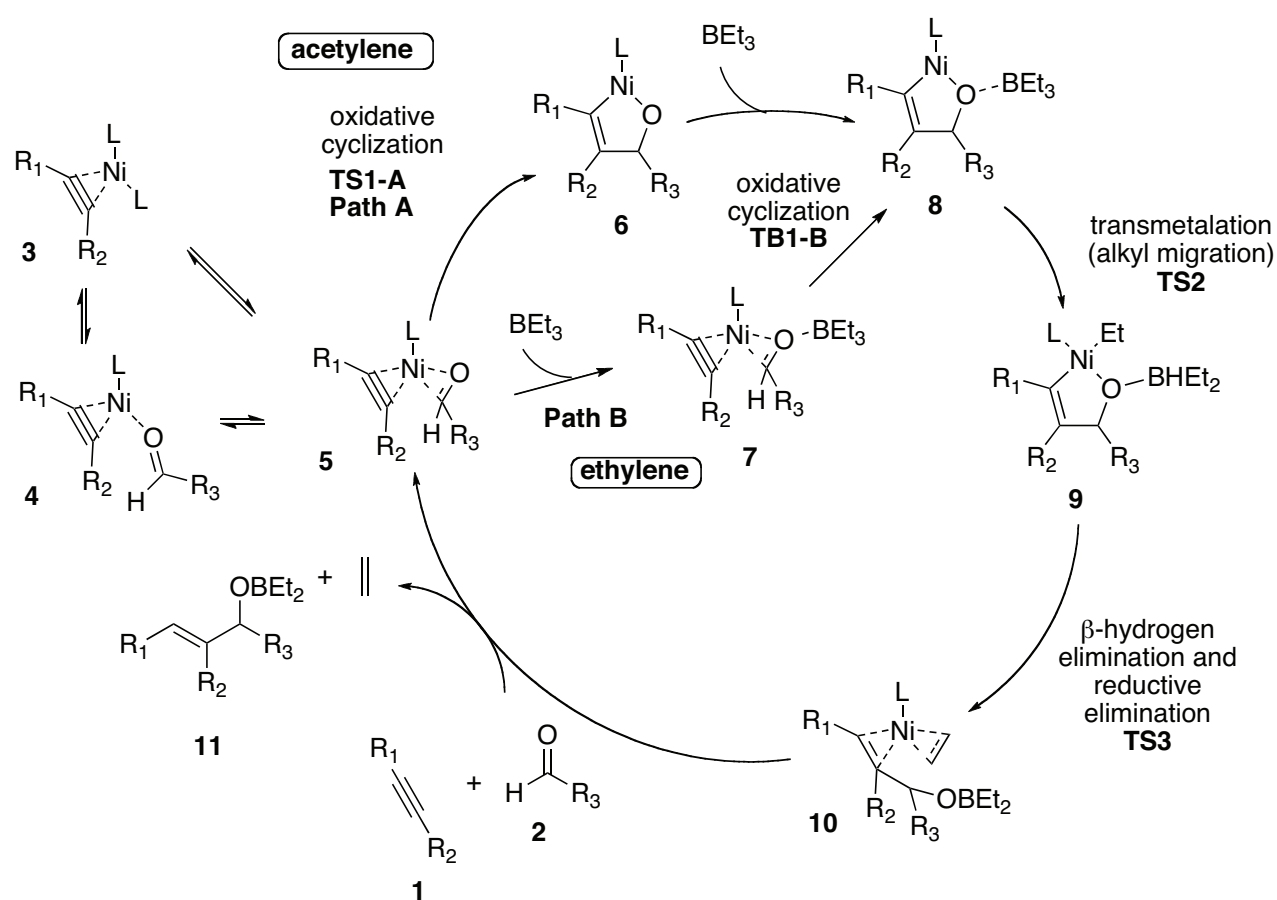
Figure 7. Examples of regioselective reductive cross-coupling reactions of alkynes with carbonyl electrophiles where TMS-substitution or  $\pi$ -conjugation do not play a role in selectivity.



Jamison and Houk *et. al.* *J. Am. Chem. Soc.* **2009**, *131*, 6654

- (a) oxidative cyclization of alkyne and aldehyde to form a metallacycle intermediate, followed by transmetalation of the reductant and subsequent reductive elimination of the product
- (b) a similar mechanism but with the metal bonded to the reductant in the oxidative cyclization
- (c) oxidative addition of the reductant to the metal and subsequent insertion of the two  $\pi$  components
- (d) oxidative addition to one  $\pi$  component (alkyne or aldehyde) and subsequent insertion of the second component.





**Figure 2.** (a) Alternative pathway of alkyne–aldehyde oxidative cyclization: borane coordination to the aldehyde oxygen. Bond lengths in Å. Energies relative to 3. Hydrogens in  $\text{BEt}_3$  have been omitted. (b) Oxidative cyclization of ethylene and acetaldehyde. Bond lengths in Å. Energies relative to the catalyst resting state, alkene(bisphosphane)nickel(0) complex 3'.

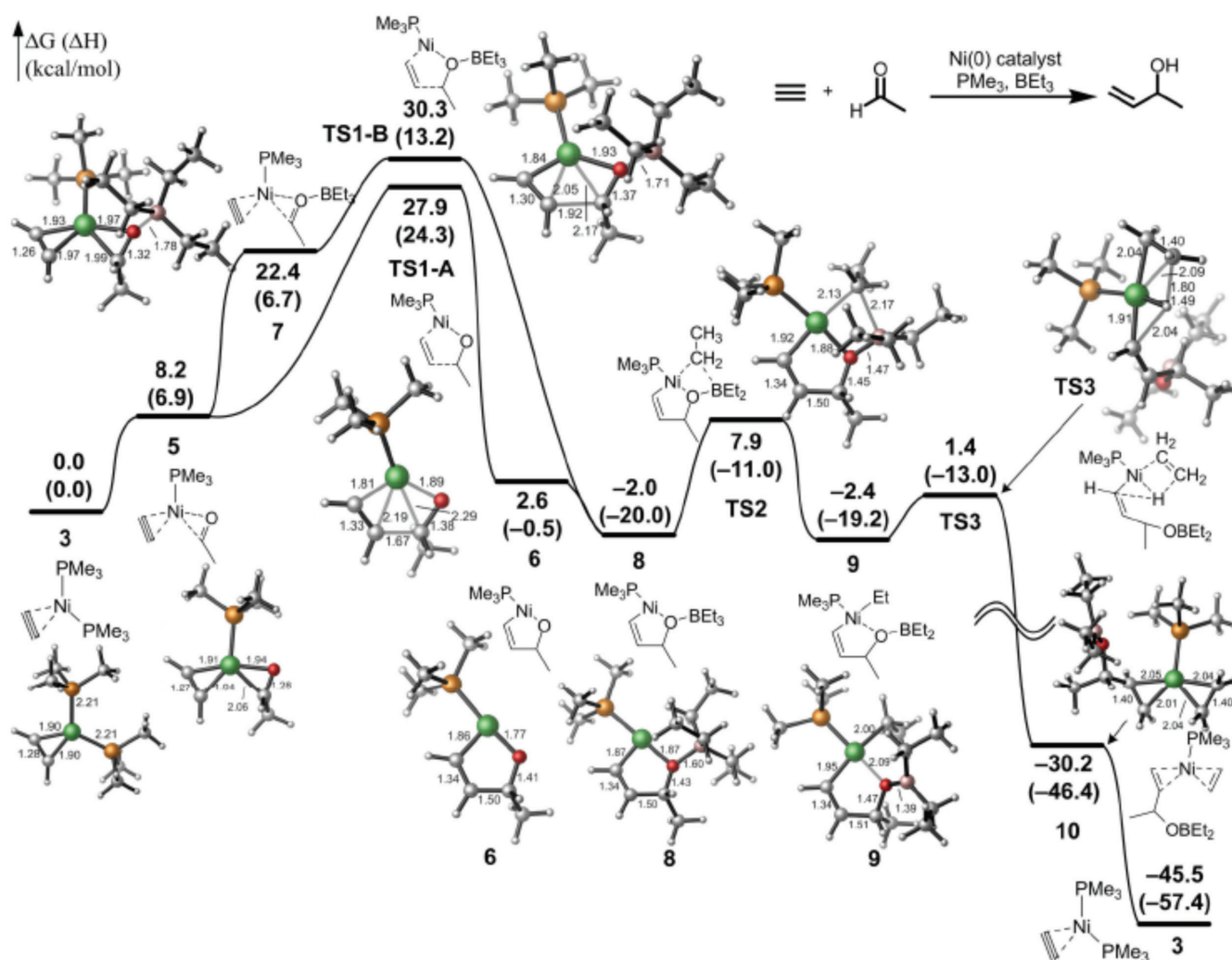
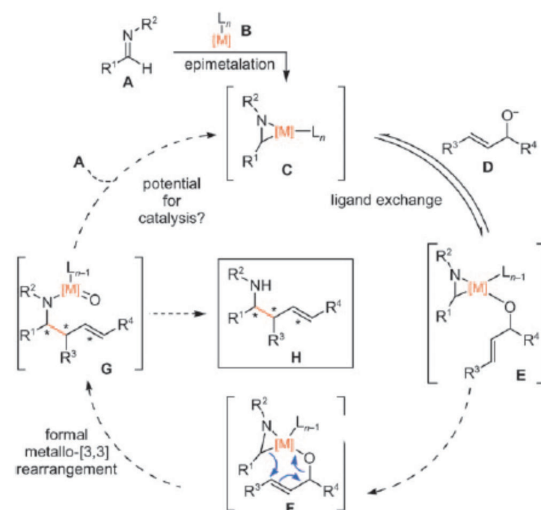


Figure S1. Free energy surface of the Ni(0)-catalyzed reductive coupling of acetylene and acetaldehyde.

### 3. Summary and Perspective

Micalizio demonstrated new type of reductive cross coupling based on the Ti mediated alkoxide directed strategy. This system is applicable to many type of reductive cross coupling and also Micalizio is also successful in to complex molecule. Further if possible....

- 1) catalytic
- 2) mechanism - ligand number and effect on Ti (transition state)



(Micalizio et.al. *Angew. Chem. Int. Ed.* **2009**, *48*, 3648.)

