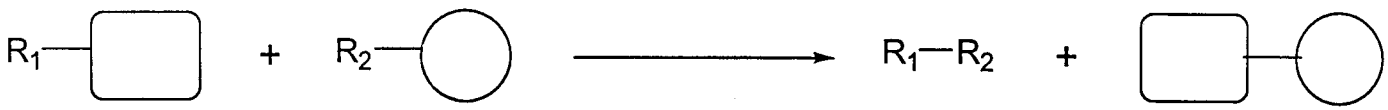
Ru Catalyzed "Atom Economical" Alkyne-Alkene Coupling Reactions

Jiping Fu
07/09/02

"Atom Economy"



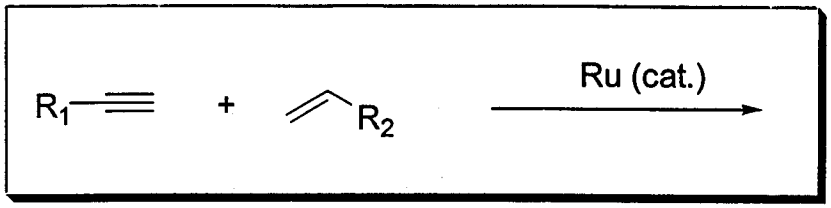
"A Search of Atom Economical Reactions"

Diels-Alder Reactions, Cycloisomerizations

Hydroformation, Hydrogenation

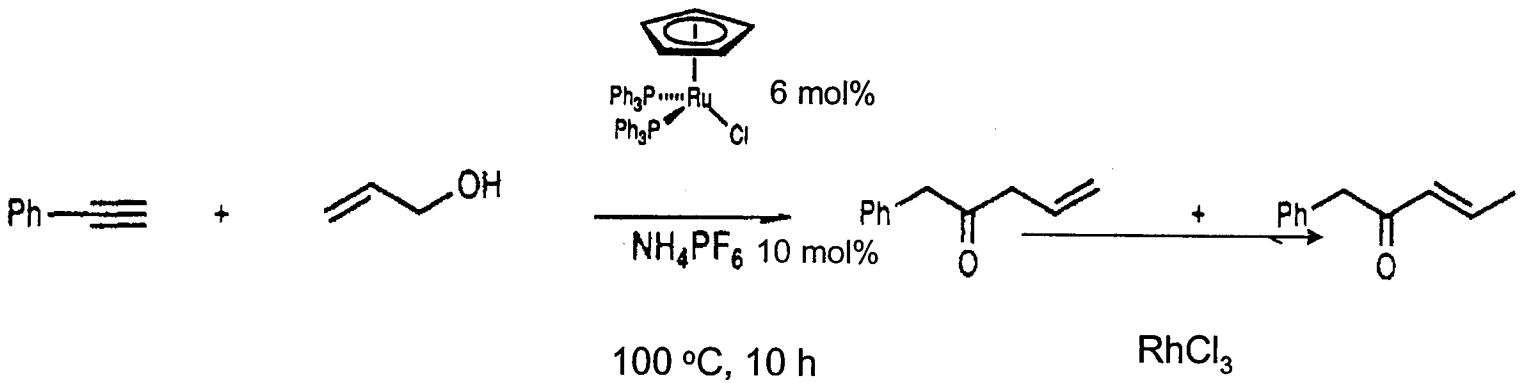
Trost, B. M. *Science* **1991**, *254*, 1471.

Invention of New Atom Economical Reactions



Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, asap.

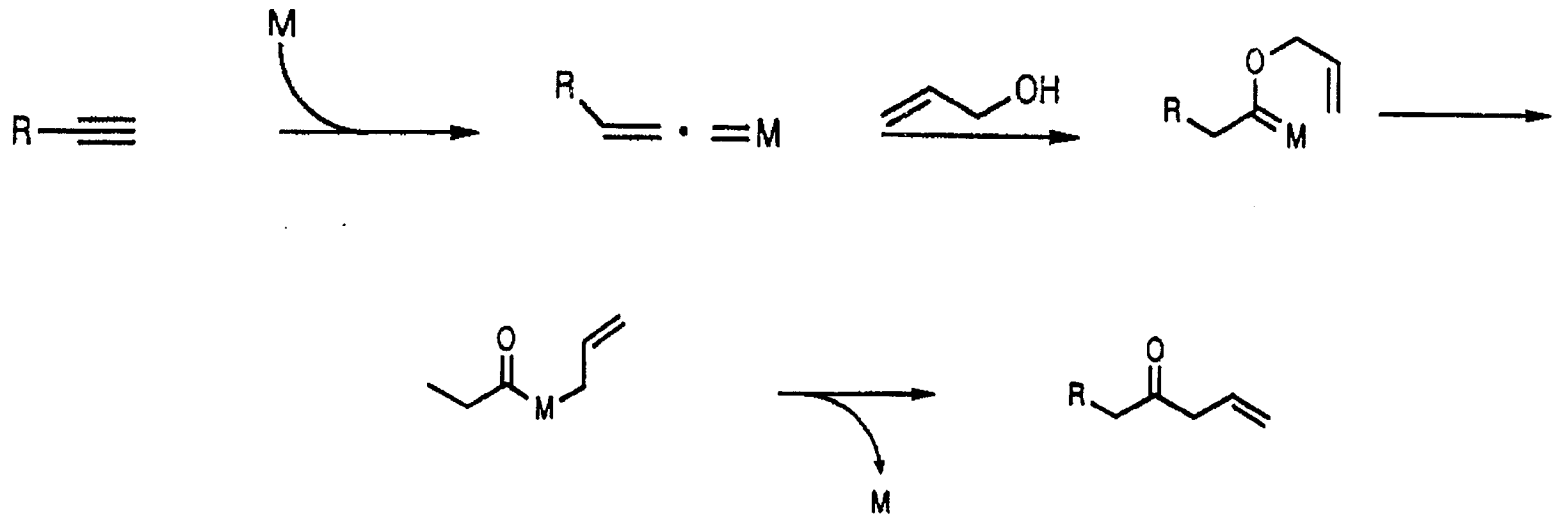
Alkyne-Allyl Alcohol Addition



Yield: 79%

Trost, B. M.; *et al J. Am. Chem. Soc.* **1990**, *112*, 7809.

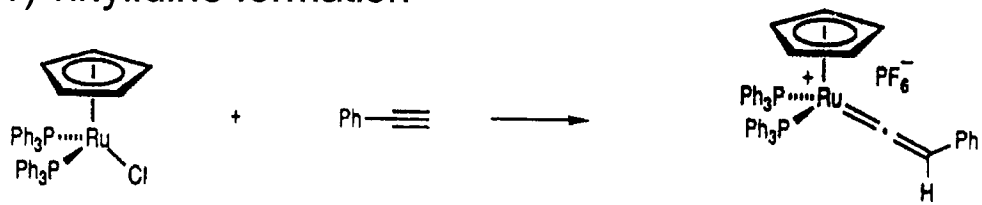
Method using stoichiometric amount of metal such as $W(CO)_n$

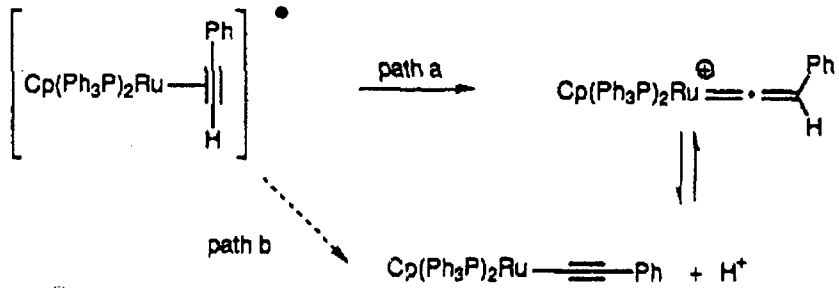


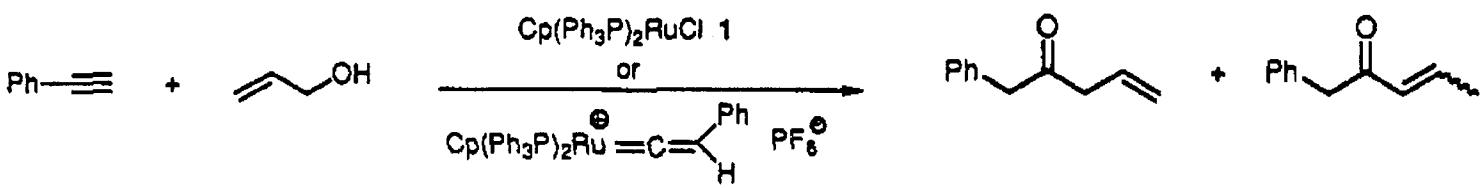
Casey, C. P.; *et al. Organometallics* **1985**, *4*, 736.

Mechanism of Addition

1) vinylidine formation







2

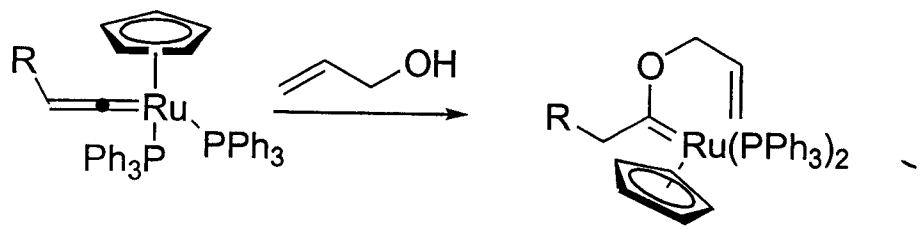
NH_4PF_6

Using either **1** or **2** as catalyst, the reaction rates and yields were identical

Trost, B.M.; *et al. J. Am. Chem. Soc.* **1992**, *114*, 5579.

Addition of Allylic Alcohols

2) addition of allyl alcohol



i) Addition of PPh_3 retarded the reaction rate

ii) Replacing the PPh_3 with chelating dppe inhibited the reaction

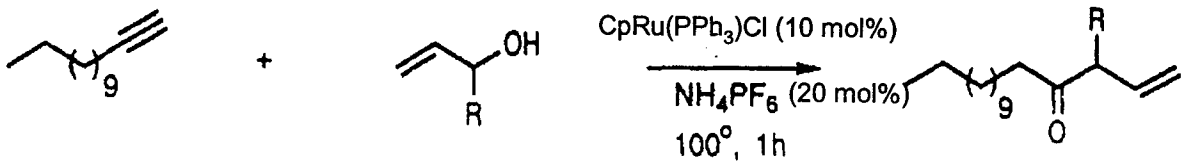
iii) Addition of ethanol to the vinylidine is very slow

iv) Methyl substituent on the olefin does not react

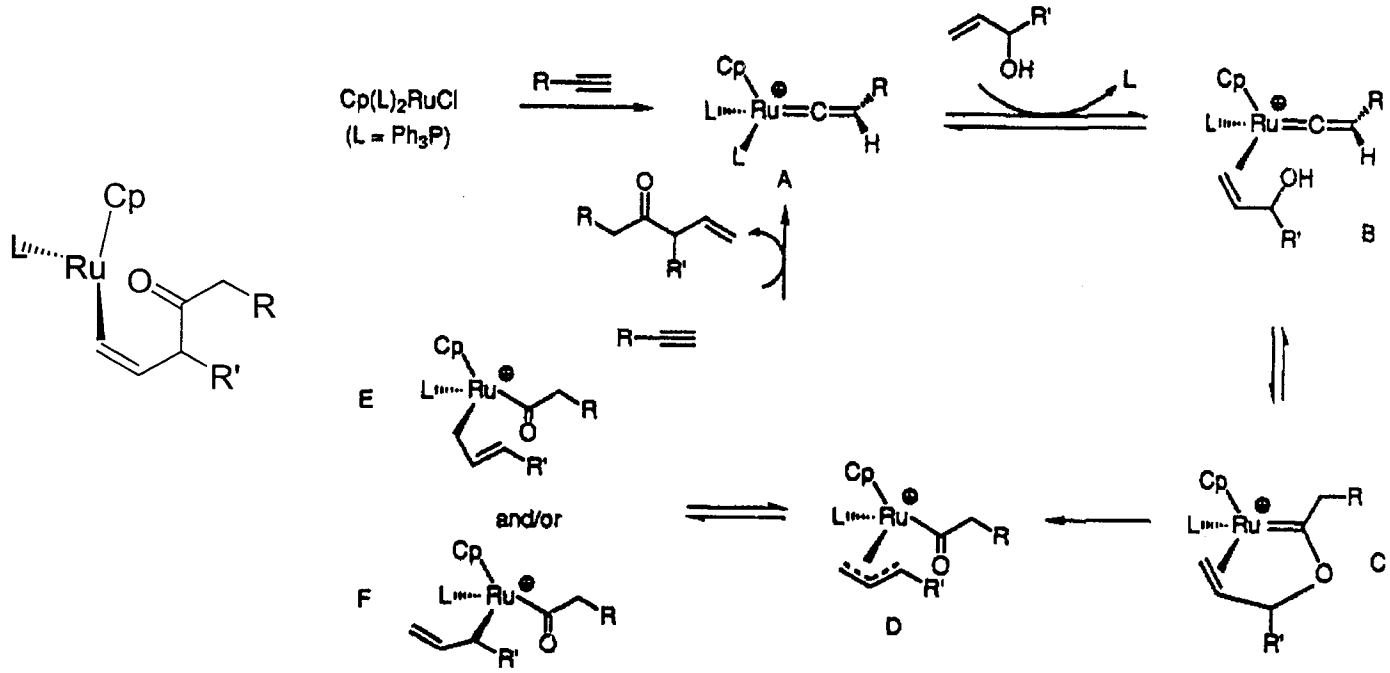
The PPh_3 must dissociate from Ru during reaction

The coordination of olefin assist the addition of alcohol

Mechanism Rational for Condensation

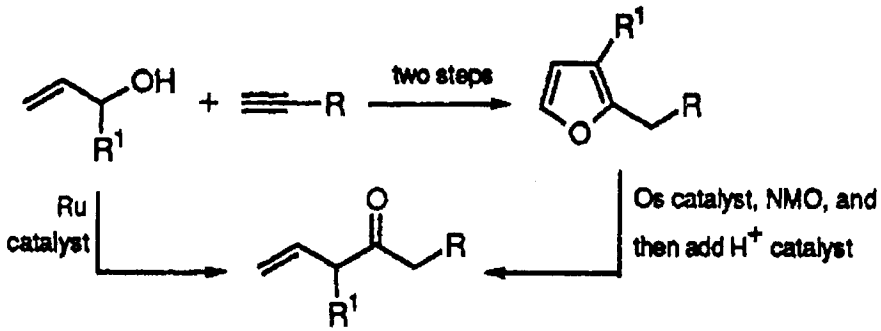


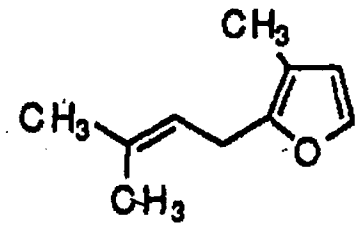
a) R = CH_3 63%
b) R = i-C_3H_7 57%



Trost, B. M. et al. J. Am. Chem. Soc. **1992**, *114*, 5579.

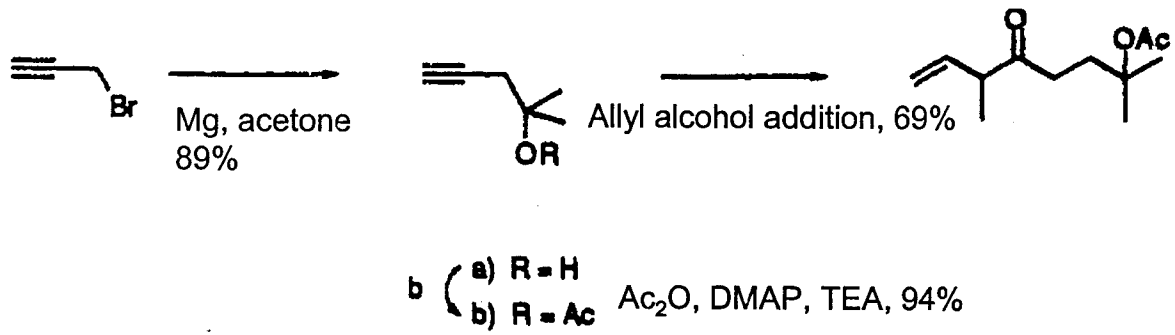
Synthesis of Furan





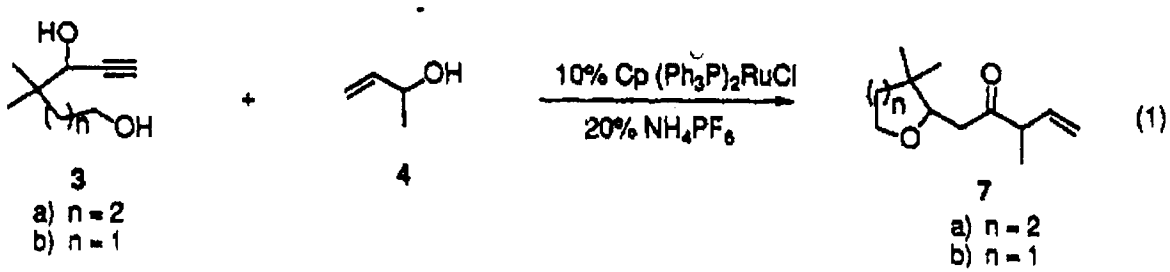
rosefuran

The most prized fragrance: oil of rose

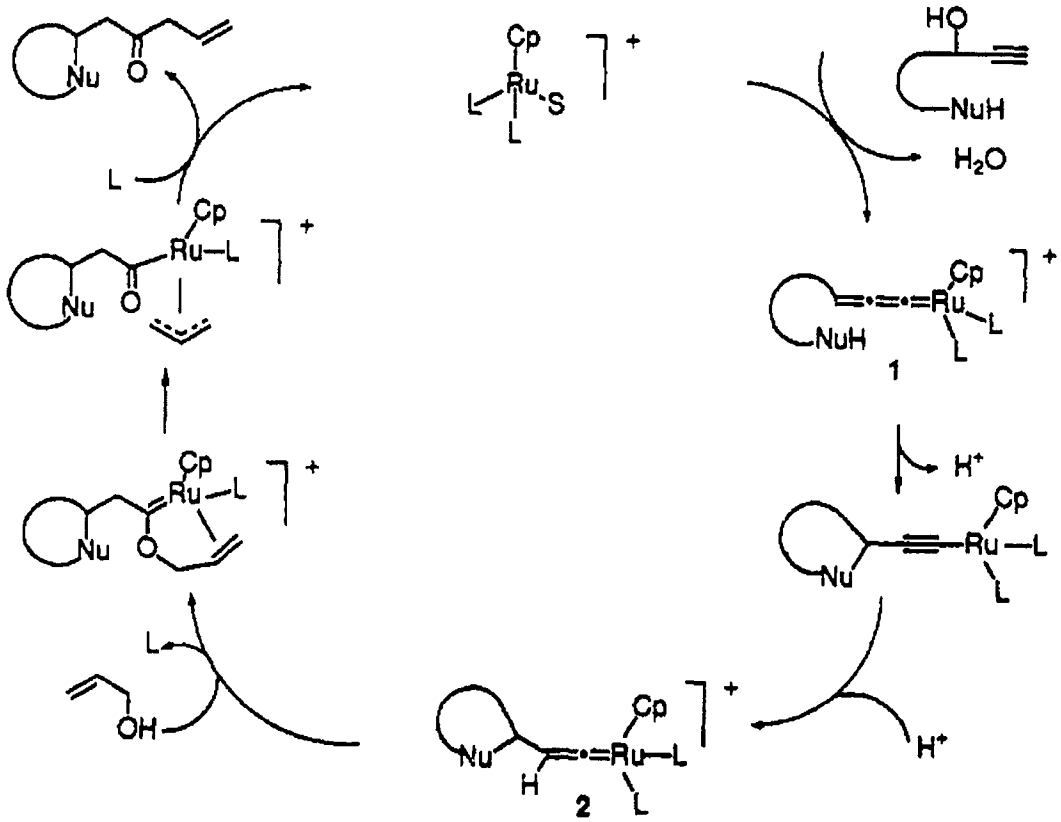


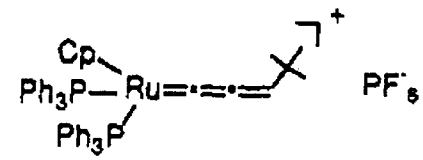
Trost, B. M., *et al. J. Org. Chem.* **1994**, *59*, 1078

Addition of Propargyl Alcohol with Allyl Alcohol



7a: 61% yield
7b: 71% yield

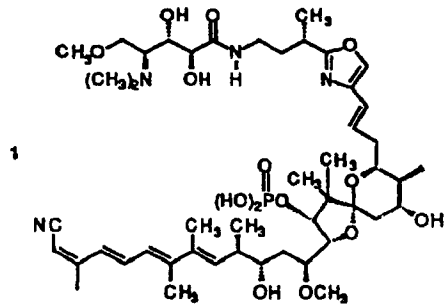




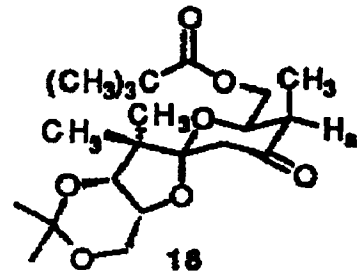
Does not react with allyl alcohol

Trost, B.M., et. al. J. Am. Chem. Soc. **1992**, *114*, 5476

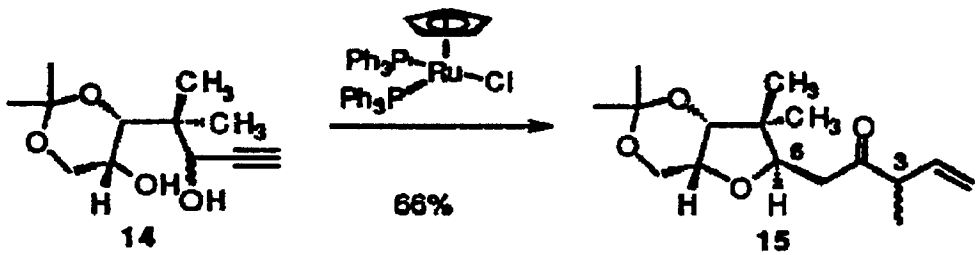
Synthesis of Spiroketal of (-)-Calyculin



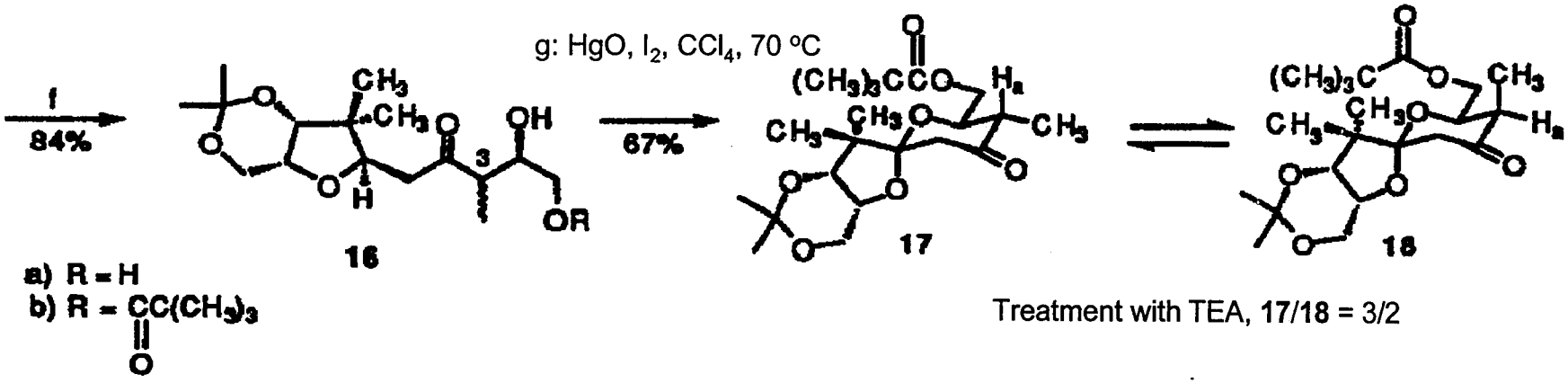
(-)-calyculin A



Spiroketal core



DHQD-PHN, $K_3Fe(CN)_6$, K_2CO_3, t-C_4H_9OH, H_2O, 0°C

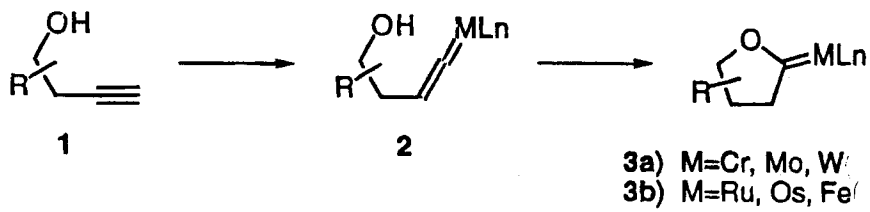


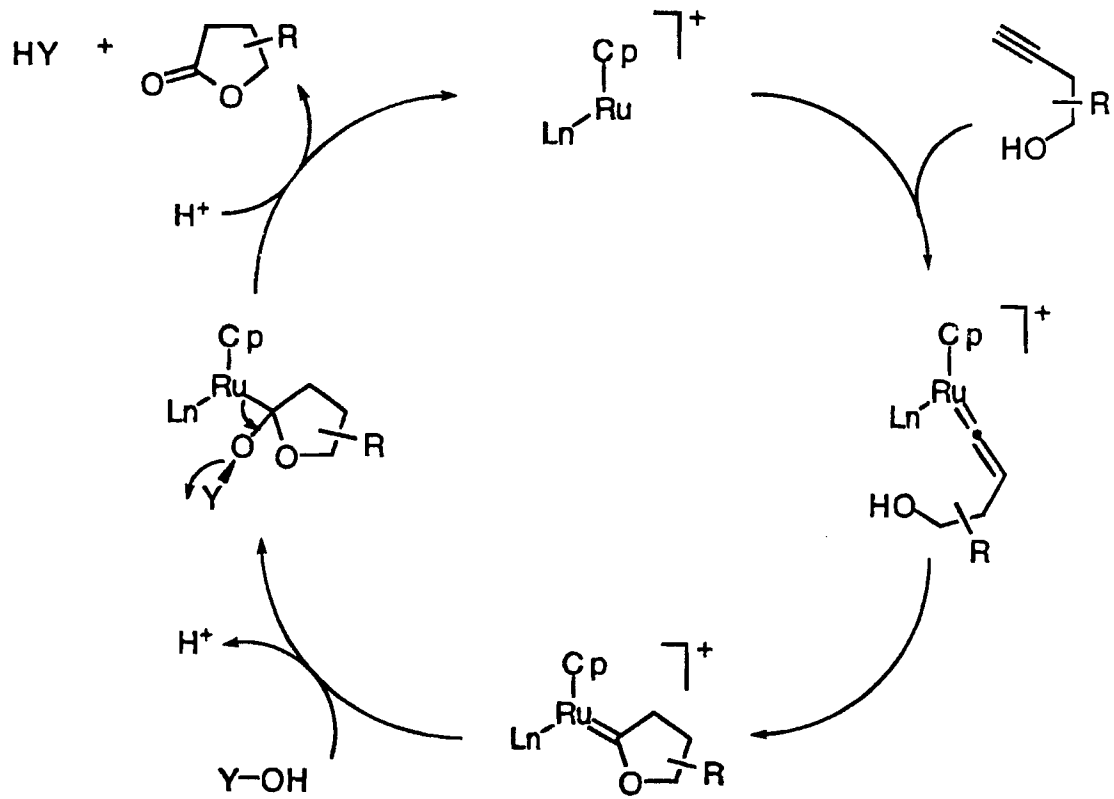
Treatment with TEA, 17/18 = 3/2

Trost, B.M.; *et al. Tetrahedron Lett.* **1994**, *35*, 4059

Cyclization of Homopropargyl Alcohols

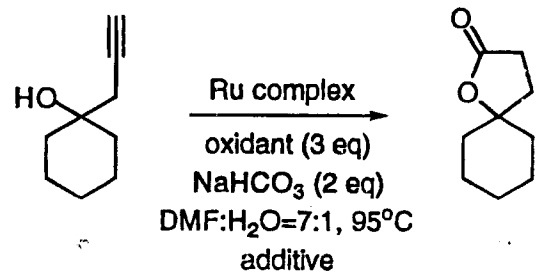
Internal addition of hydroxy group





Trost, B. M.; *et al. J. Am. Chem. Soc.* **1999**, *121*, 11680

Cyclization Optimization

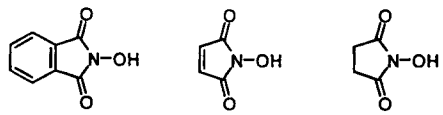


Ru complexs: $CpRuL_2Cl$

Reaction optimization:

1) Oxidant

H_2O_2, t-BuOOH, mCPBA, pyridine N-oxide
DMSO no reaction



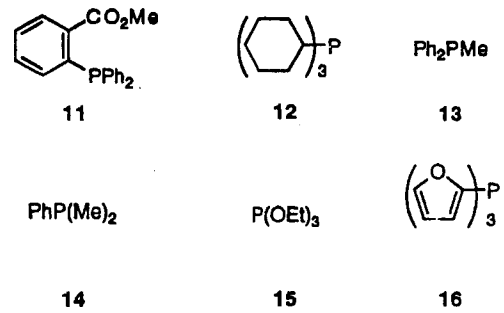
7 8 9

9 gave the highest yield

2) additives

No additive yield 17%
45% additive BuN_4PF_6 yield 60%

3) Phosphine ligands



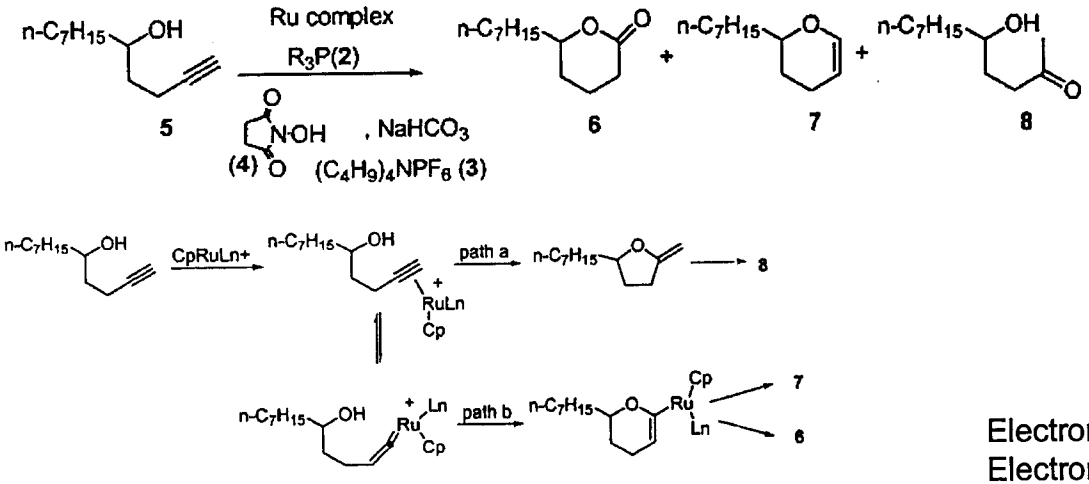
11 12 13 14 15 16

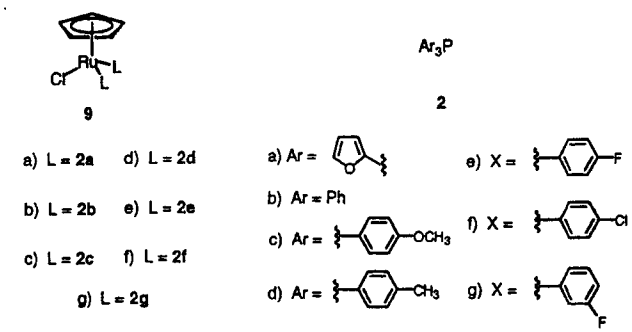
Bulky, electron rich ligands decreased rate
Small, electron poor ligands increased rate

the rate determining step---addition step

Optimized reaction condition:
7 mol% CpRu(COD)Cl, 10 mol% **16**, 45 mol% BuN_4PF_6, 3.0 equiv **9**, $NaHCO_3$, DMF/H_2O,
Yield 73-73%.
71

Cyclization of Bishomopropargyl Alcohol





Electron donating group favored formation of **6**
Electron withdrawing group favored formation of **7**

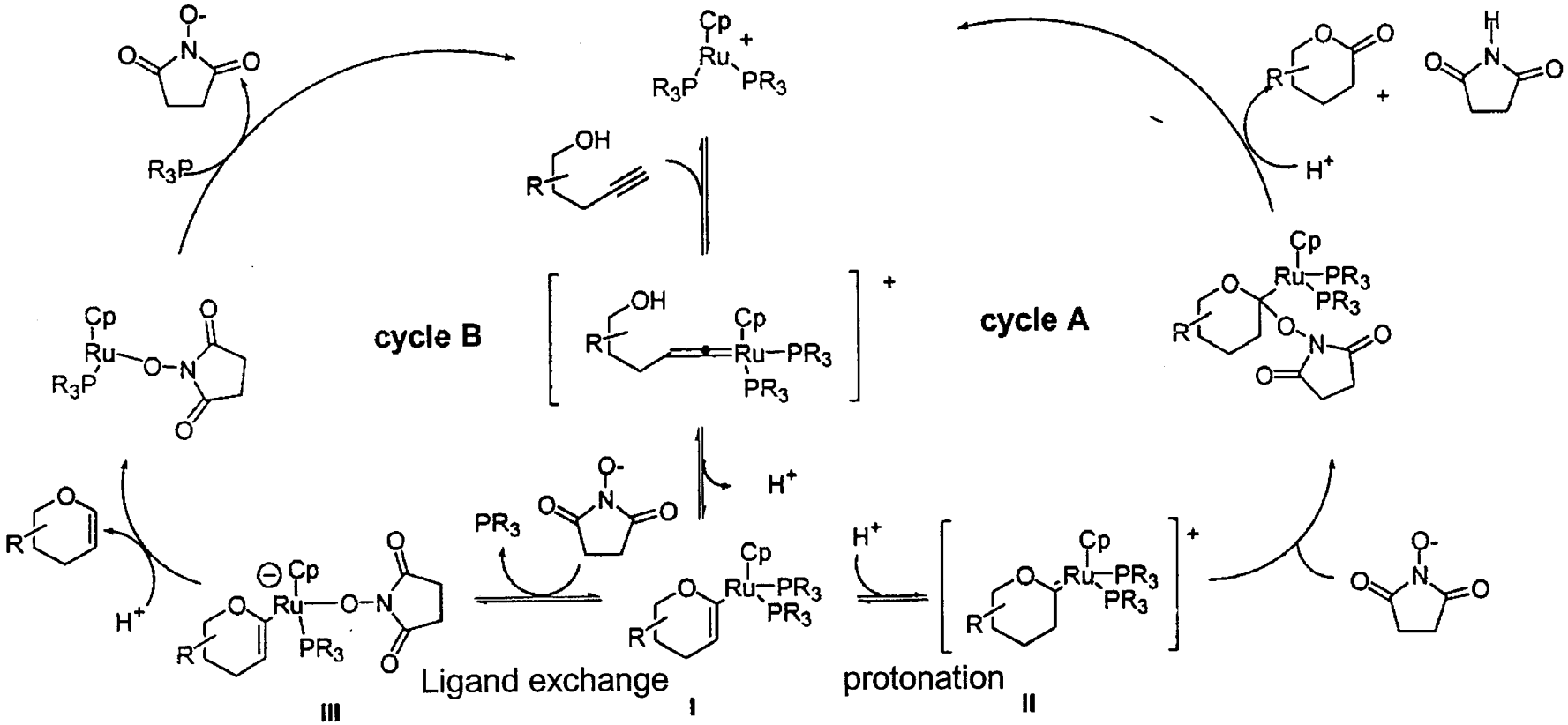
Table 1. Optimization of Oxidative Cyclization and Cycloisomerization[a]

entry	Ru complex (mol %)	ligand (mol %)	4 (mol %)	time (h)	conversion (%)	yield 6[a] (isolated yield)	yield 7[b] (isolated yield)	
1	**9a** (10%)	**2a** (20%)	300[c]	15	100	20%	33%	
2	**9a** (10%)	**2a** (40%)	300[c]	17	100	25%	31%	
3	**9a** (10%)	**2a** (60%)	300[c]	25	80	17%	24%	
4	**9b** (10%)	**2b** (40%)	300[c]	20	100	38% (34%)	40 (35%)	Electron donating ligand
5	**9c** (10%)	**2c** (40%)	300[c]	17	100	60% (57%)	20% (17%)	
6	**9d** (10%)	**2d** (40%)	300[c]	17	100	51%	23%	
7	**9e** (10%)	**2e** (40%)	300[c]	17	100	19% (16%)	57% (52%)	Electron withdrawing ligand
8	**9f** (10%)	**2f** (40%)	300[c]	26	91	13%	56%	
9	**9g** (10%)	**2g** (40%)	300[c]	26	81	9%	53%	
10	**9c** (10%)	**2c** (40%)	450[c]	20	100	(65%)	(11%)	Stoichiometry of **4**
11	**9c** (10%)	**2c** (40%)	600[c]	23	100	(69%)	(7%)	
12	**9c** (10%)	**2c** (40%)	1000[c]	28	46	(30%)	(trace)	
13	**9c** (5%)	**2c** (20%)	600[d]	28	73	(45%)	(6%)	
14	**9e** (10%)	**2e** (40%)	200[d]	17	100	(11%)	(60%)	
15	**9e** (7.5%)	**2e** (30%)	100[d]	20	100	(7%)	(61%)	
16	**9e** (5%)	**2e** (20%)	50[d]	25	99	(4%)	(64%)	
17	**9e** (5%)	**2e** (20%)	25[d]	25	84	(5%)	(53%)	

[a] All reactions were run at 0.4 M bis-homopropargylic alcohol in DMF at 85 °C with 200 mol % $NaHCO_3$ unless otherwise noted. [b] Yield determined by gas chromatography with *n*-tetradecane as an internal standard, except where indicated it was an isolated yield. [c] *N*-Hydroxysuccinimide used. [d] Preformed sodium salt of *N*-hydroxysuccinimide used, and sodium bicarbonate was not added.

Trost, B. M.; *et al. J. Am. Chem. Soc.* **2002**, *124*, 2528.

Mechanism of Divergence



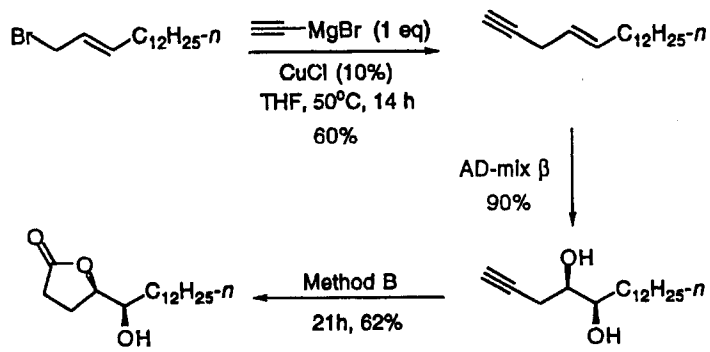
Electron withdrawing ligand

Substoichiometric amount of sodium N-hydroxysuccinimide salt

Electron donating ligand

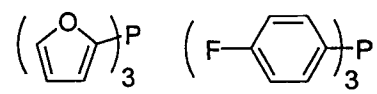
Excess of N-hydroxysuccinimide

Applications in Synthesis

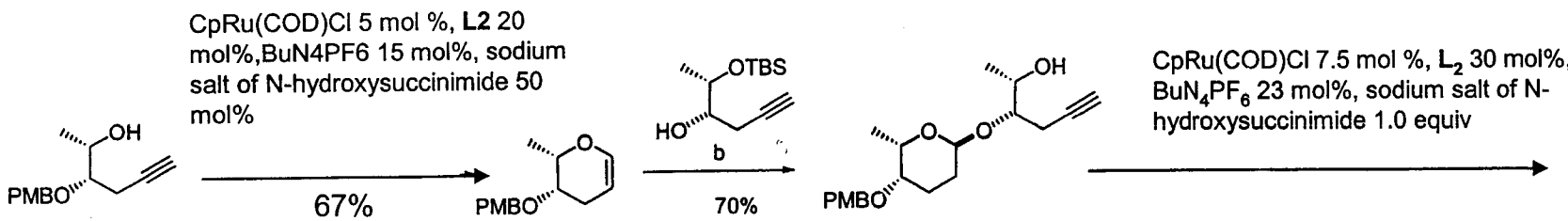


94% ee Antitumor activity

Cyclization condition: 10 mol% CpRu(COD)Cl, 15 mol% **L1**, 30 mol% BuN_4PF_6, 3.0 equiv hydroxysuccinimide, NaHCO3, DMF/H2O,

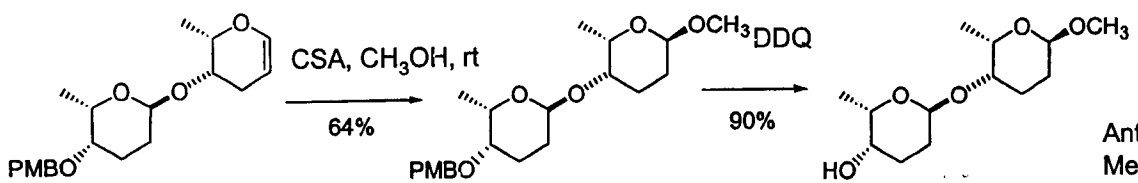


L_1 L_2



CpRu(COD)Cl 5 mol %, **L2** 20 mol%,BuN4PF6 15 mol%, sodium salt of N-hydroxysuccinimide 50 mol%

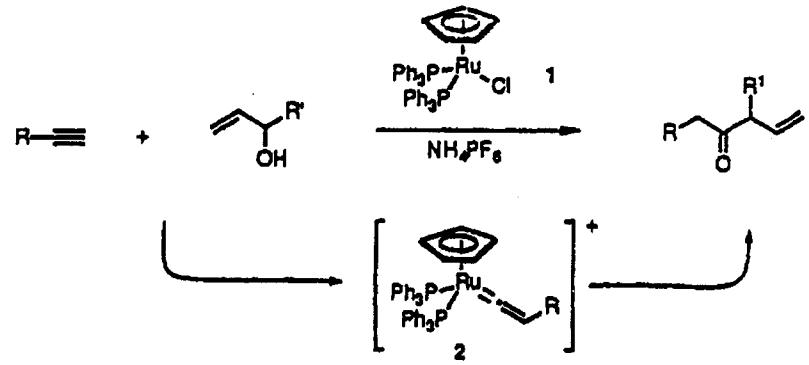
CpRu(COD)Cl 7.5 mol %, L_2 30 mol%, BuN_4PF_6 23 mol%, sodium salt of N-hydroxysuccinimide 1.0 equiv

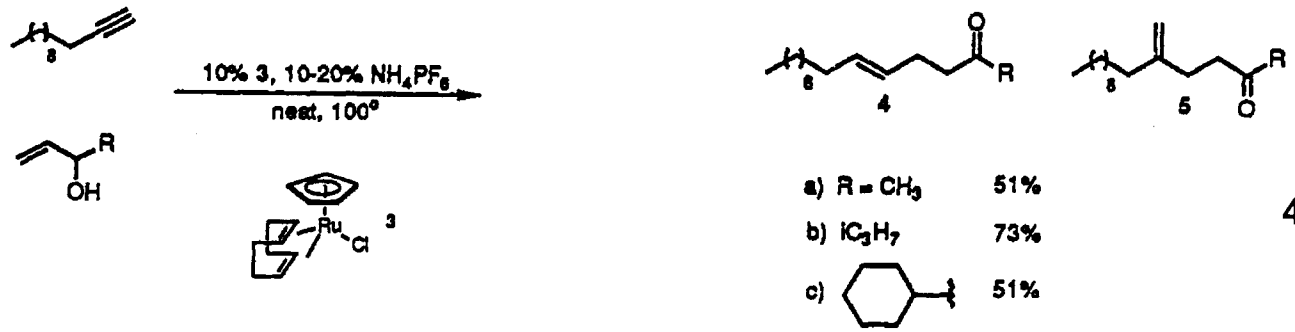


Antiviral secondary Metabolite from streptomyces

Narbosine B

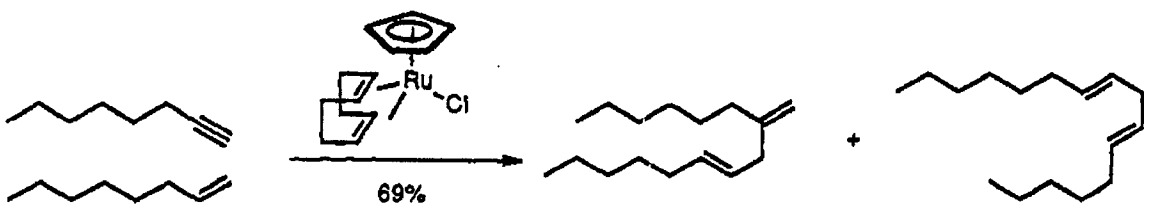
Reaction Catalyzed by Ru(COD)





4/5 = 1/1

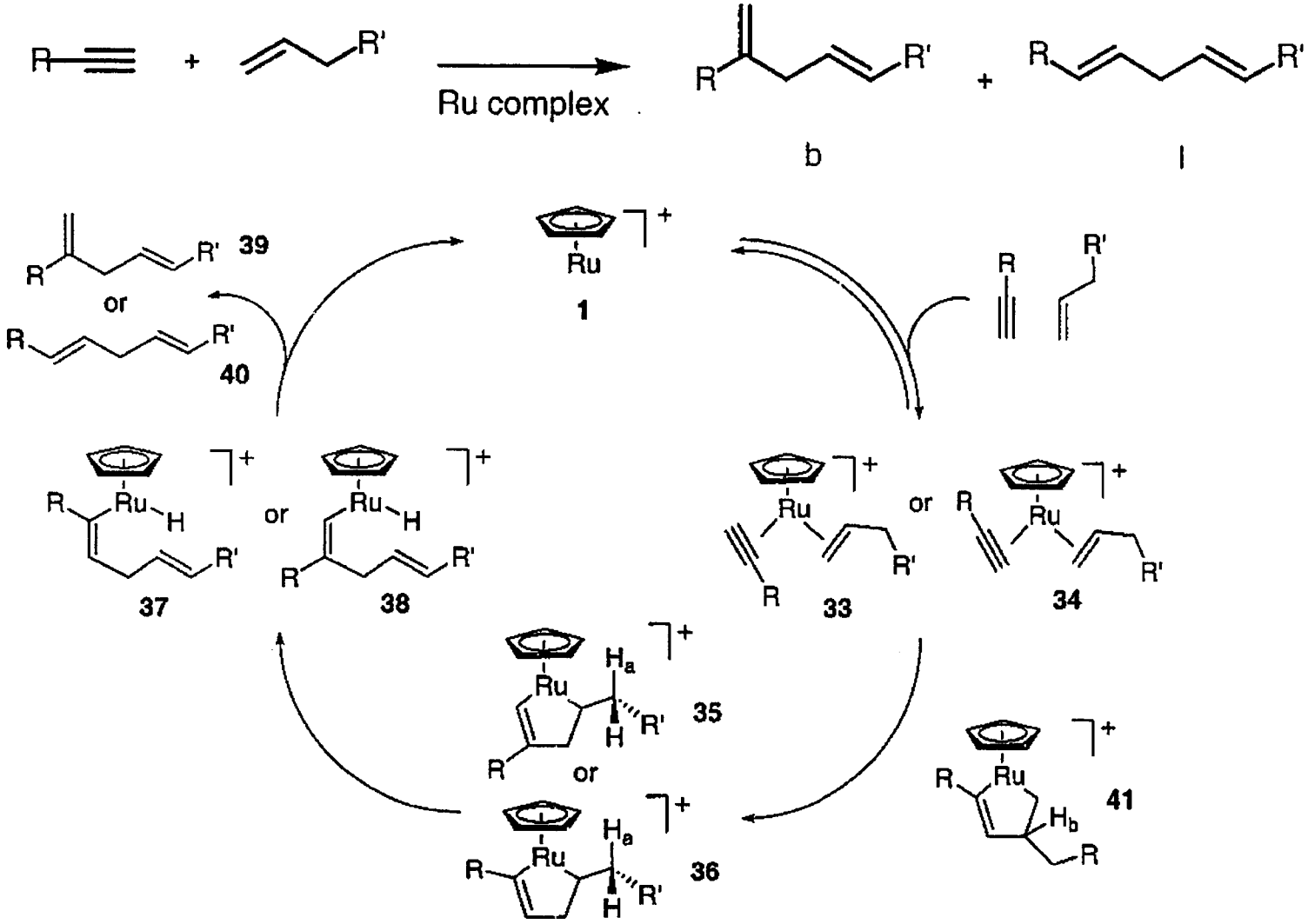
3 does not form vinylilidine with alkynes



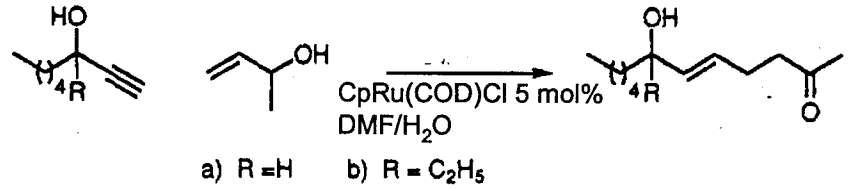
= 5/1

Trost, B. M.; *et al. J. Am. Chem. Soc.* **1993**, *115*, 10402.
Trost, B. M.; *et al. J. Am. Chem. Soc.* **1993**, *115*, 4361

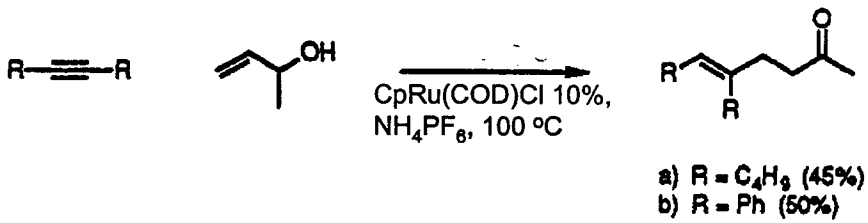
Alkyne-Alkene Addition

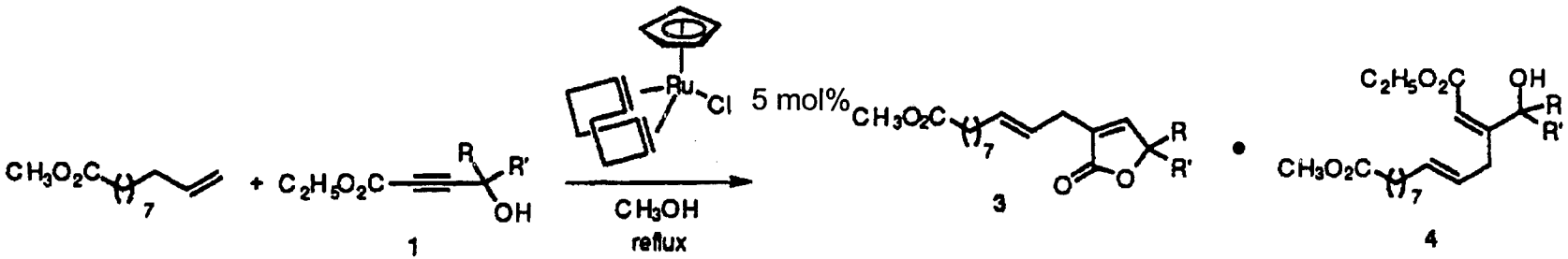


Selective Synthesis of Linear Product



50-60% yield

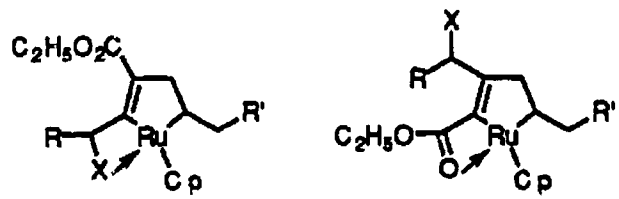




a) R = R' = H — Yield: 51%, 3/4 = 2.9/1

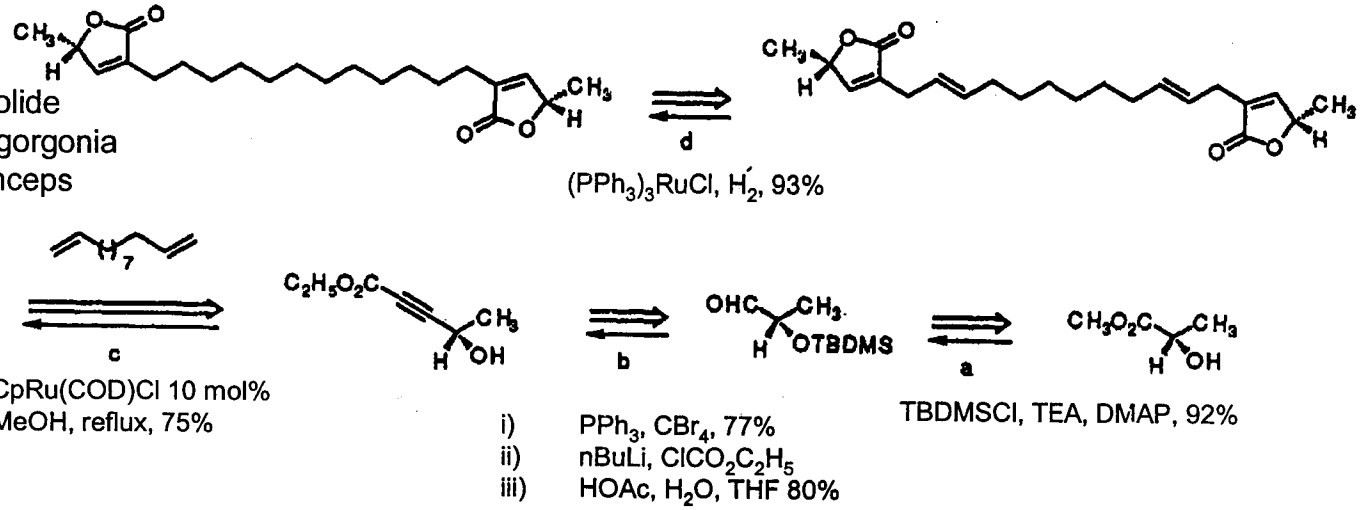
b) R = H, R' = iC3H7 — Yield: 63%, 3/4 = 4.4/1

c) R, R' = (CH2)4 — Yield: 67%, 3/4 = 12.2/1

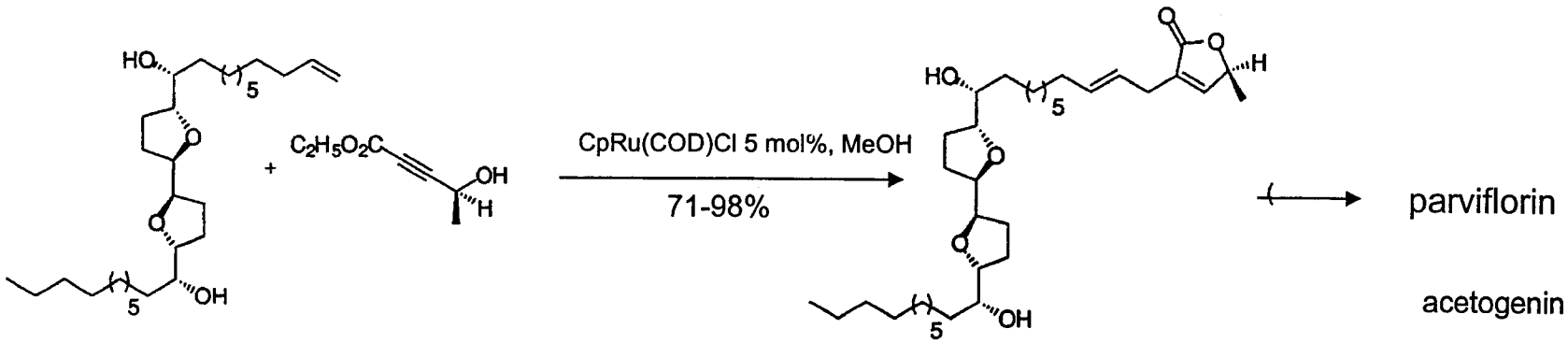


Synthesis of (+)-Ancepsenolide

(+)-Ancepsenolide
Isolated from gorgonia
pterogorgia anceps

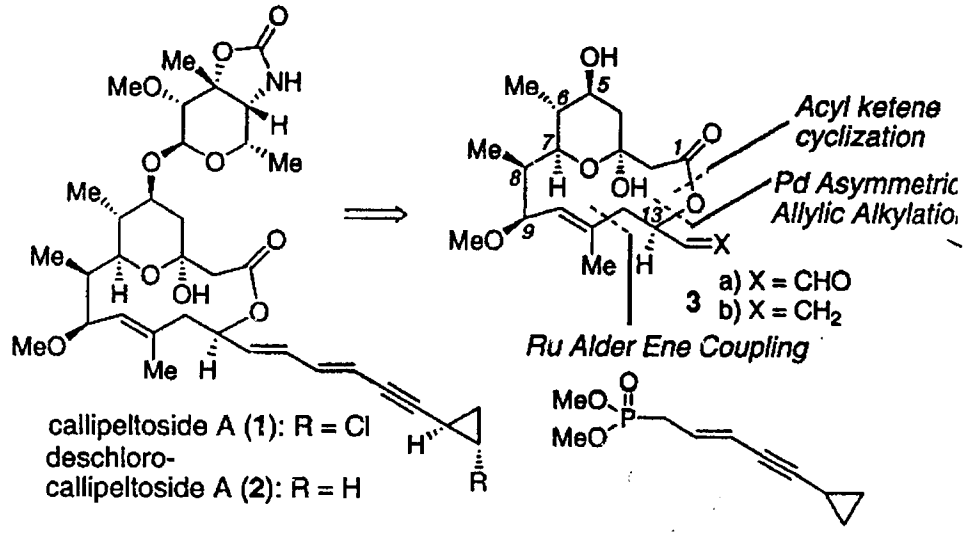


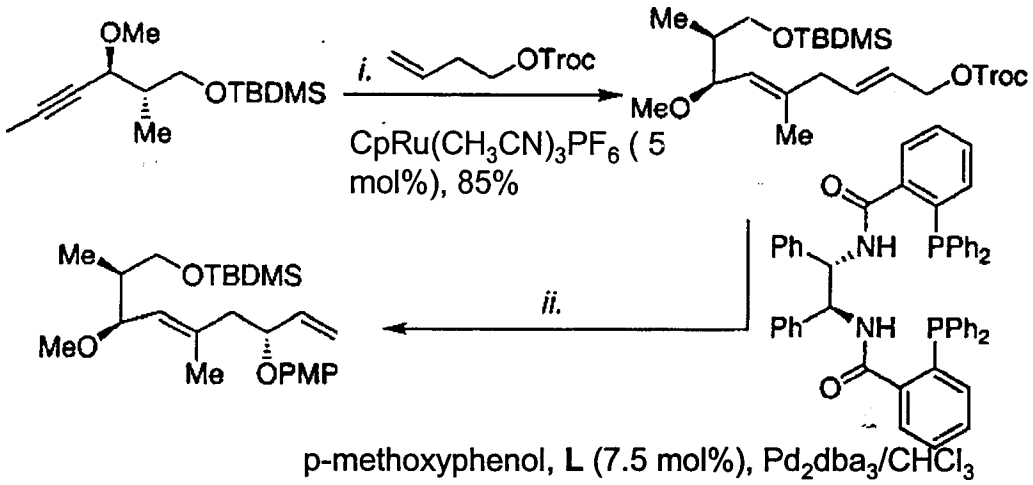
Trost, B. M.; *et al. J. Am. Chem. Soc.* **1994**, *116*, 4985

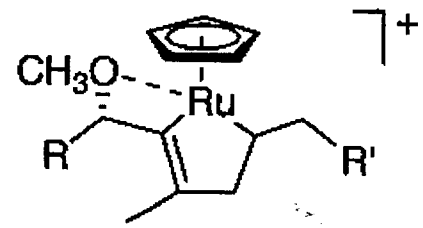


Trost, B. M.; *et al. Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2632.

Synthesis of Deschlorocallipeltoside A

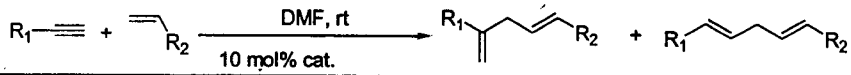


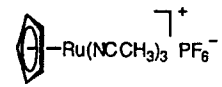




Trost, B.M. *et al. J. Am. Chem. Soc.* **2001**, *123*, 9499.

Selective Synthesis of Branched Products

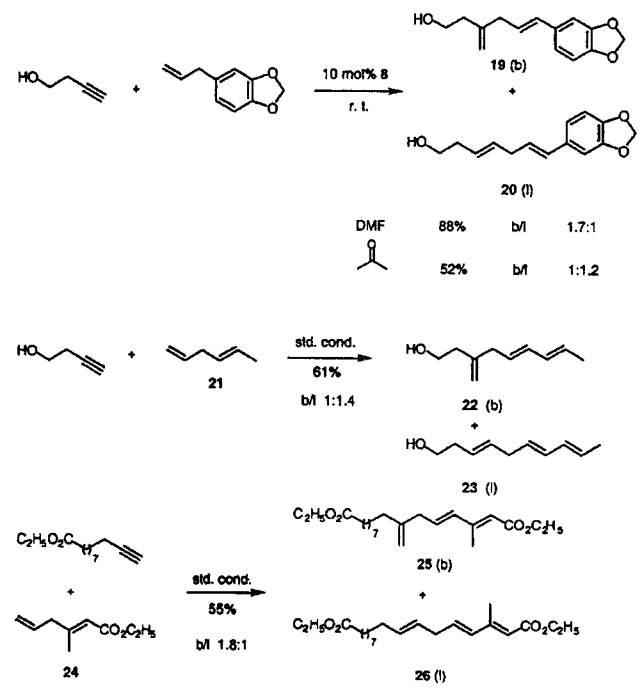




Cat.

Entry	Alkyne	Alkene	Product	Isolated Yield	b/l
1				86%	4.8 : 1
2				74%	5.3 : 1
3				72%	7.2 : 1
4				62%	7.4 : 1
5				73%	7.4 : 1
6				66%	8.9 : 1
7				82%	8.9 : 1
8				69%	9.1 : 1
9				75%	9.7 : 1
10				74%	9.8 : 1
11				73%	10.5 : 1
12				68%	10.5 : 1
13				75%	11.3 : 1
14				69%	14.2 : 1
15				84%	15.3 : 1
16				72%	16.7 : 1
17				58%	17.4 : 1
18				59%	>25 : 1
19				67%	>25 : 1
20				25%	>25 : 1
21				72%	>25 : 1
22				84%	>25 : 1

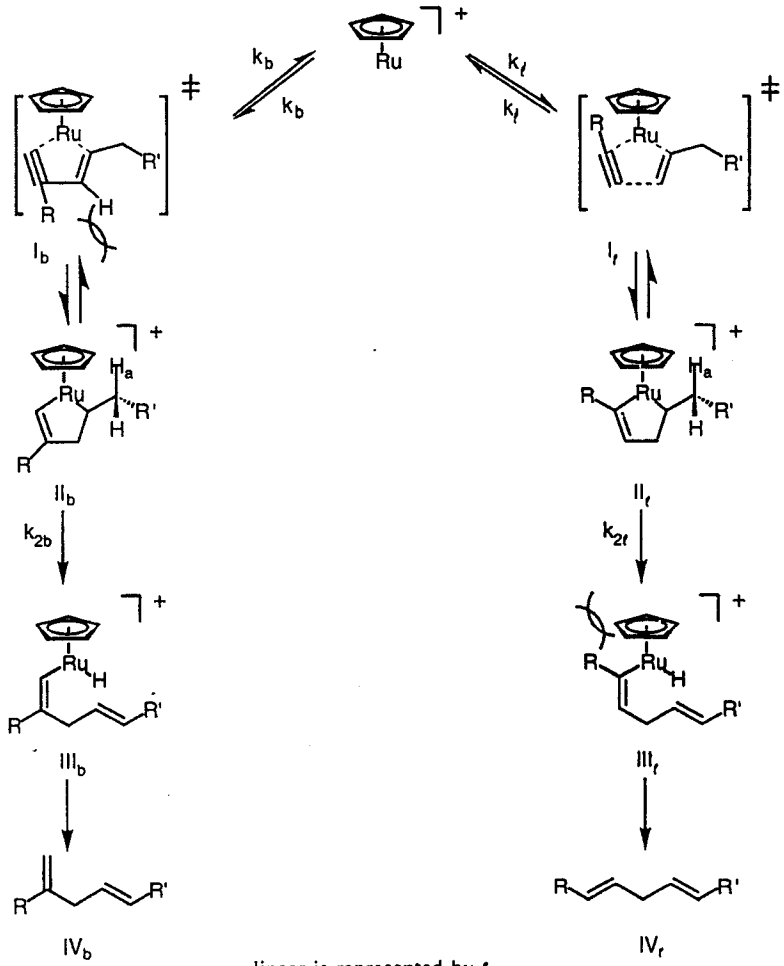
Scope of reactions



Trost, B. M.; *et al. J. Am. Chem. Soc.* **2001**, *123*, 12504.

Product: Branch VS Linear

Scheme 2. Competitive Ruthenacycle Formation and β-Hydrogen Elimination

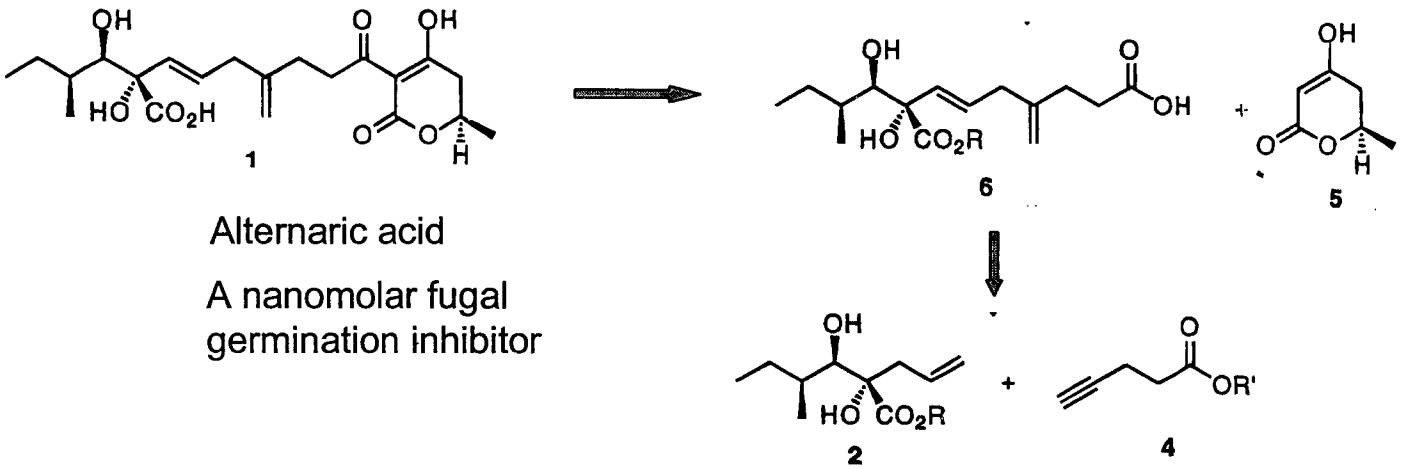


linear is represented by ℓ

Linear product:

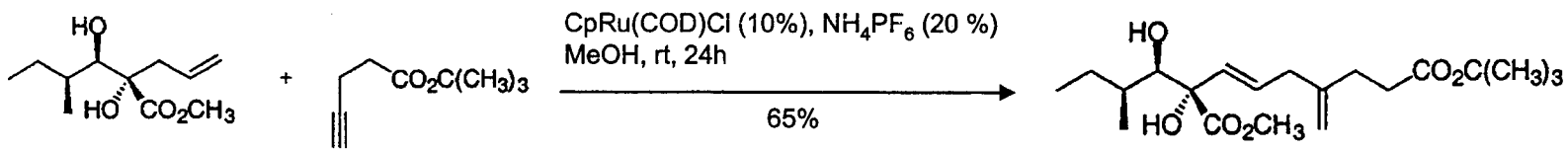
Rate of β-hydrogen elimination faster than the reversal of metallacycle

Synthesis of Alternaric Acid



Alternaric acid

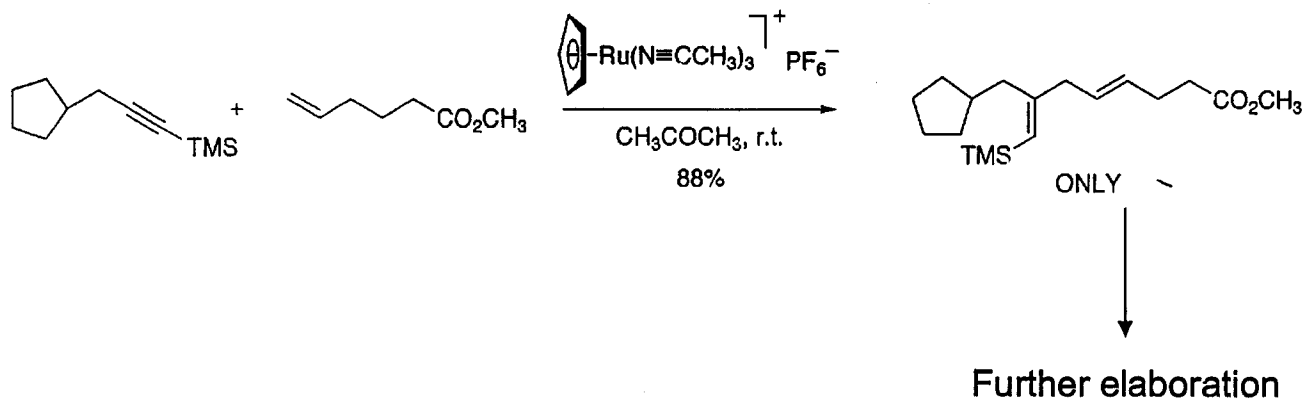
A nanomolar fugal germination inhibitor

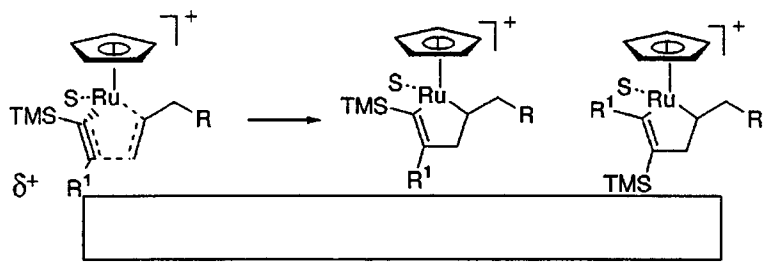


b/l 12.5 : 1

Trost, B. M.; *et al. J. Am. Chem. Soc.* **1998**, *120*, 9228.

Synthesis of Tri-substituted Alkenes



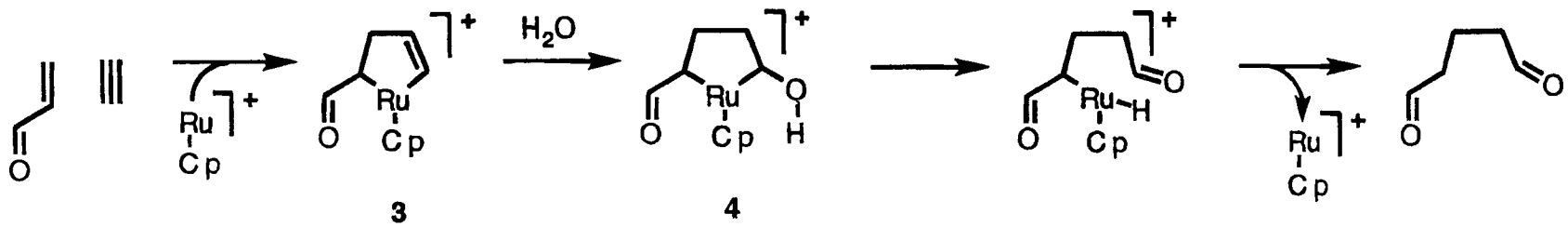


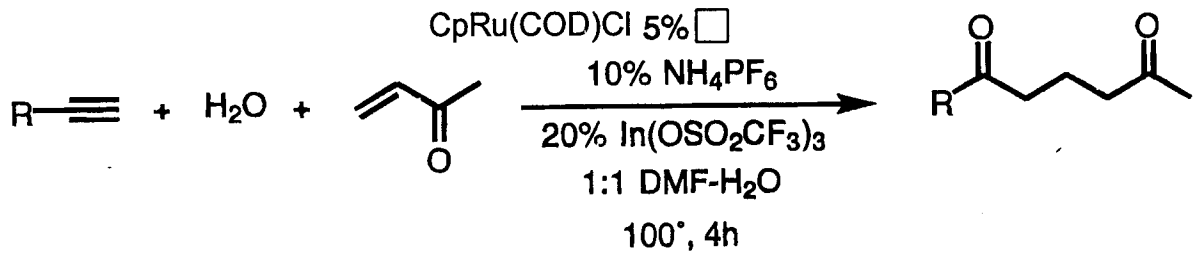
Silicon stabilizing the forming C-Ru bond.

The ability of silicon to stabilize a positive charge b to itself may induce a polarization of alkyne-ruthenium cationic complex and thus subsequent nucleophilic attack by alkene.

Trost, B. M.; *et al Org. Lett.* **2000**, *2*, 1761.

Three Component Synthesis of Diketone



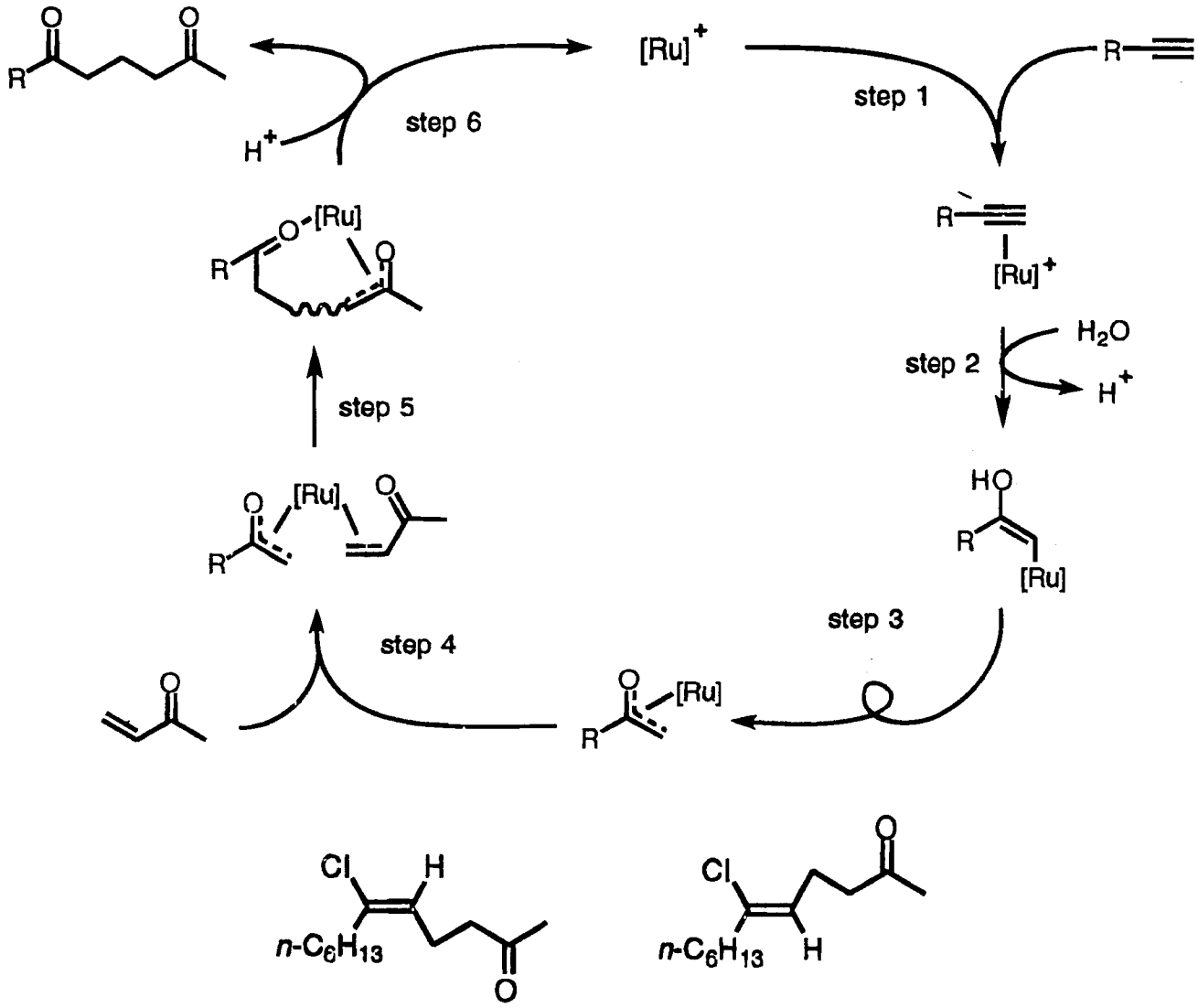


R = C_6H_{13}

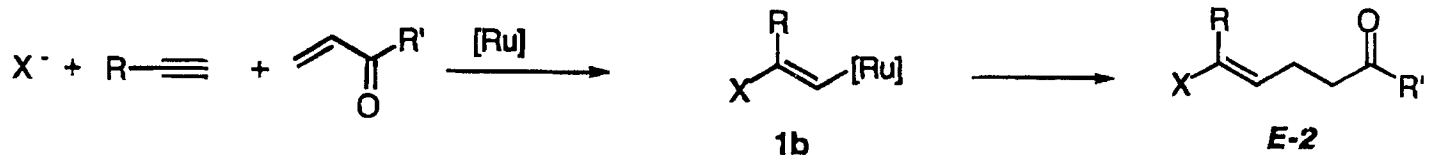
additive	yield
none	43%
10 mol% $InCl_3$	50%
10 mol% $In(OSO_2CF_3)_3$	67%
20 mol% $In(OSO_2CF_3)_3$	74%

Trost, B. M.; *et al. J. Am. Chem. Soc.* **1997**, *119*, 836.

Enolate Mechanism



Vinylchloride



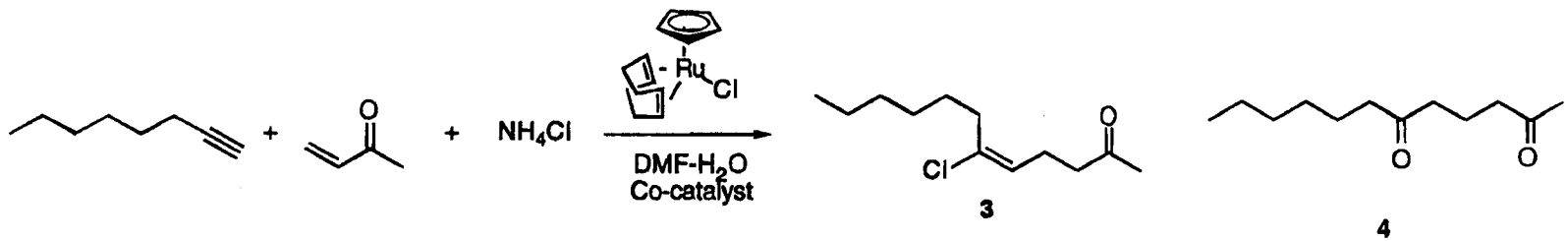


Table 1. Selected Optimization Experiments for Equation 2[a]

entry	[Ru]	cocatalyst (mol %)	NR_4Cl (eq)	DMF−H_2O ratio	[Alkyne] (M)	temp °C	isol. yield **3**	isol. yield **4**
1	5.0	$InCl_3$(15)	1.1 (R = H)	9:1	0.25	100	14	24
2	5.0	$AlCl_3 \cdot 6H_2O$(15)	1.1 (R = H)	9:1	0.25	100	34	19
3	10.0	$AlCl_3 \cdot 6H_2O$(15)	1.1 (R = H)	9:1	0.25	100	25	42
4	10.0	$AlCl_3 \cdot 6H_2O$(30)	1.1 (R = H)	9:1	0.25	100	39	52
5	10.0	$AlCl_3 \cdot 6H_2O$(15)	2.2 (R = H)	9:1	0.25	100	44	28
6	10.0	$AlCl_3 \cdot 6H_2O$(15)	3.3 (R = H)	20:1	0.25	100	45	16
7	10.0	$SnCl_4 \cdot 5H_2O$(15)	3.3 (R = H)	20:1	0.25	100	48	2
8	10.0	$SnCl_4 \cdot 5H_2O$(15)	3.3 (R = H)	20:1	0.50	100	56	4
9	10.0	$SnCl_4 \cdot 5H_2O$(15)	3.3 (R = H)	20:1	1.00	100	45[b]	17
10	10.0	$SnCl_4 \cdot 5H_2O$(15)	3.3 (R = H)	20:1	0.50	60	72[c]	5
11	10.0	$SnCl_4 \cdot 5H_2O$(15)	3.0 (R = CH_3)	NA[d]	0.50	60	72	trace
12	10.0	none	3.3 (R = H)	9:1	0.25	100	11	10

[a] All reactions were run according to eq 2 with 1:2 ratio of alkyne to MVK. [b] *E*:*Z* ratio of 6.2. [c] *E*:*Z* ratio of 6.0. [d] NA = not applicable since only was DMF employed.

Trost, B. M.; *et al. J. Am. Chem. Soc.* **1999**, *121*, 1988.

Vinylbromide

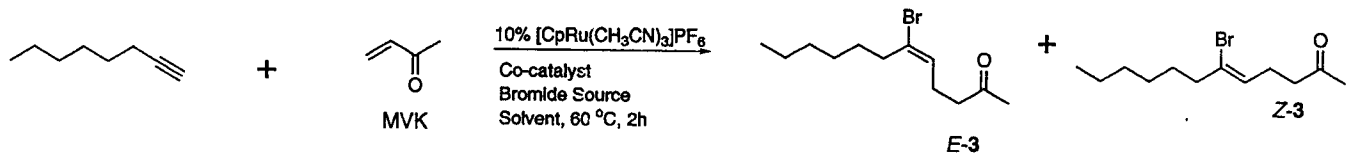
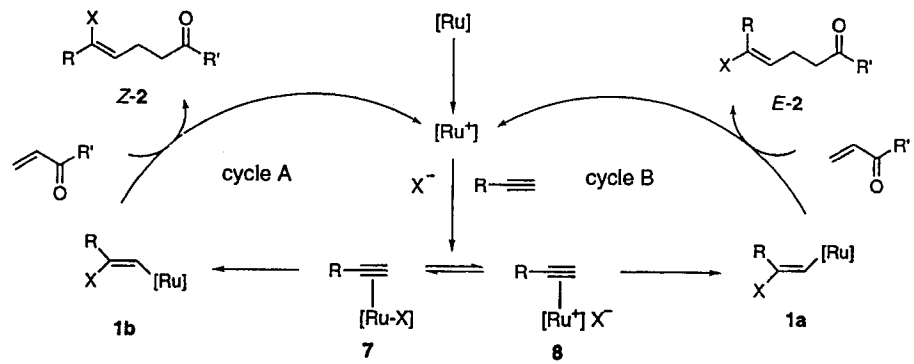


Table 1. Selected optimization experiments for (*Z*)-vinyl bromide formation [Eq. (2)].[a]

Entry	Co-catalyst (mol %)	Bromide source (equiv)	Solvent	Yield of **3** [%]	*Z*/*E*[b]
1	$SnBr_2$ (15)	NH_4Br (3)	DMF	13	1/3.3
2	$SnBr_4$ (15)	NH_4Br (3)	DMF	54	1/2.1
3	$SnBr_4$ (15)	NH_4Br (3)	acetone/DMF 1/1	71	1/2.3
4	$SnBr_4$ (15)	$N(CH_3)_4Br$ (3)	acetone/DMF 1/1	54	4.0/1
5	$SnBr_4$ (15)	$N(CH_3)_4Br$ (3)	acetone	35	15/1
6	$SnBr_4$ (15)	NH_4Br (3)	acetone	40	10/1
7	$SnBr_4$ (15)	NH_4Br (3)	acetone/DMF 2/1	62	1/2.2
8	$SnBr_4$ (15)	NH_4Br (3)	acetone/DMF 4/1	56	1.4/1
9	$SnBr_4$ (15)	LiBr (3)	acetone	81	4.0/1
10	$SnBr_4$ (15)	LiBr (1.5)	acetone	88	6.6/1
11	$SnBr_4$ (5)	LiBr (1.5)	acetone	54	6.7/1
12	none	LiBr (1.5)	acetone	22	4.2/1

[a] All reactions run according to Equation (2) with a 1:1.5 ratio of alkyne to MVK and a concentration of 0.5 M in alkyne. [b] Determined by ^{1}H NMR spectroscopy or GC.

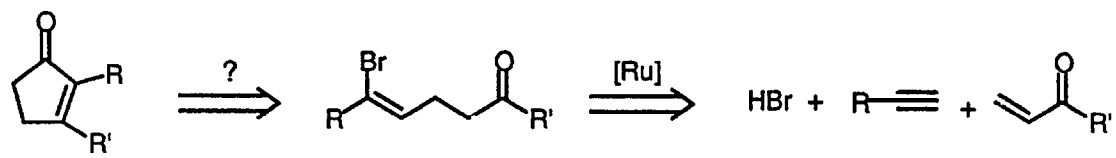


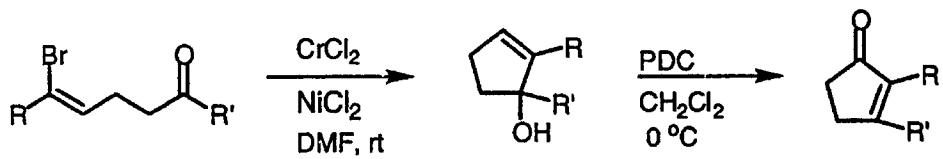
Scheme 1. Proposed mechanism for the ruthenium-catalyzed, stereoselective synthesis of vinyl bromides. Selection of cycle A or B is dependent upon the nature of the solvent and the concentration of halide in solution.

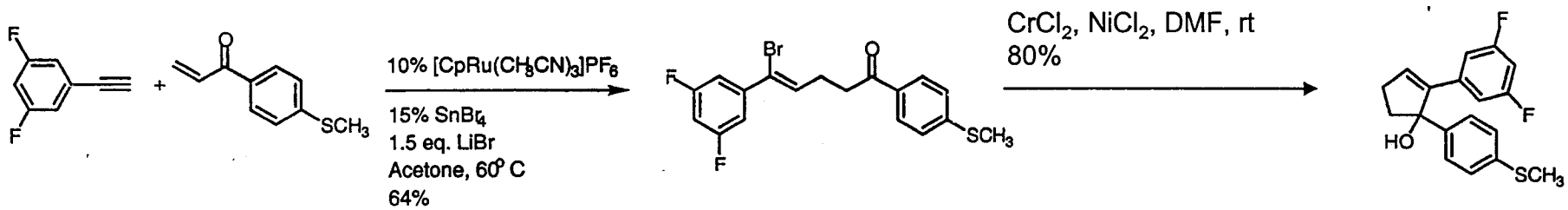
8 more ionic -> external addition
7 more covalent -> internal addition

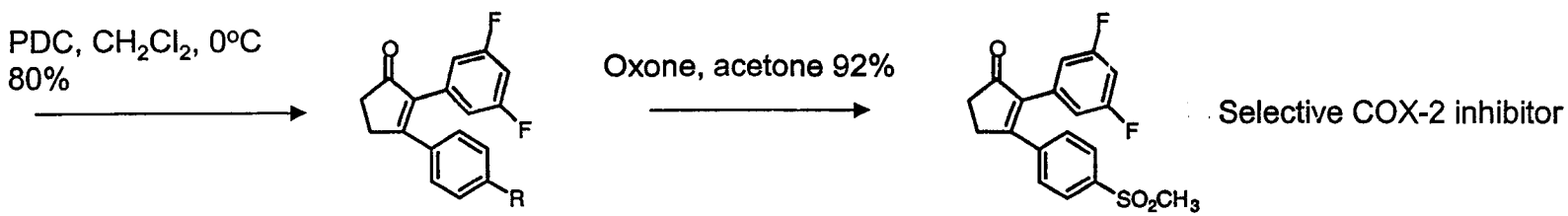
Trost, B. M.; *et al. Angew. Chem., Int. Ed.* **2000**, *39*, 360.
Trost, B. M.; *et al. J. Am. Chem. Soc.* **2002**, *124*, 7376.

Synthesis of Cyclopentanoids









Selective COX-2 inhibitor

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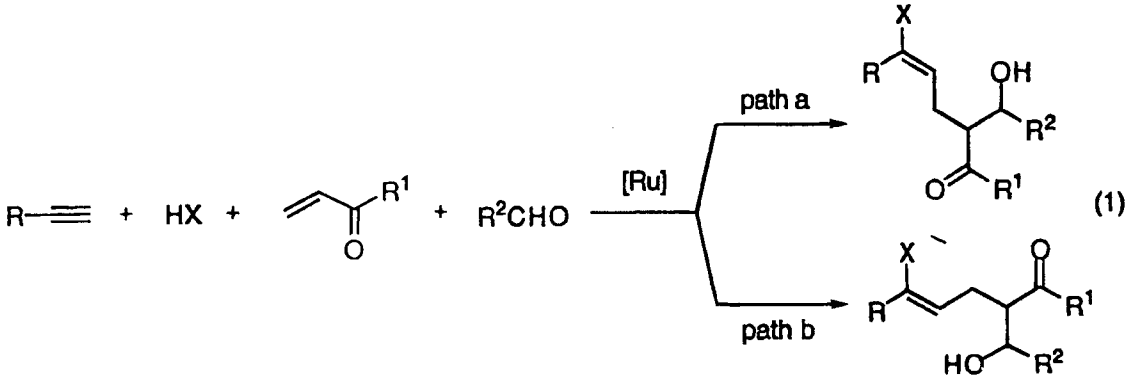
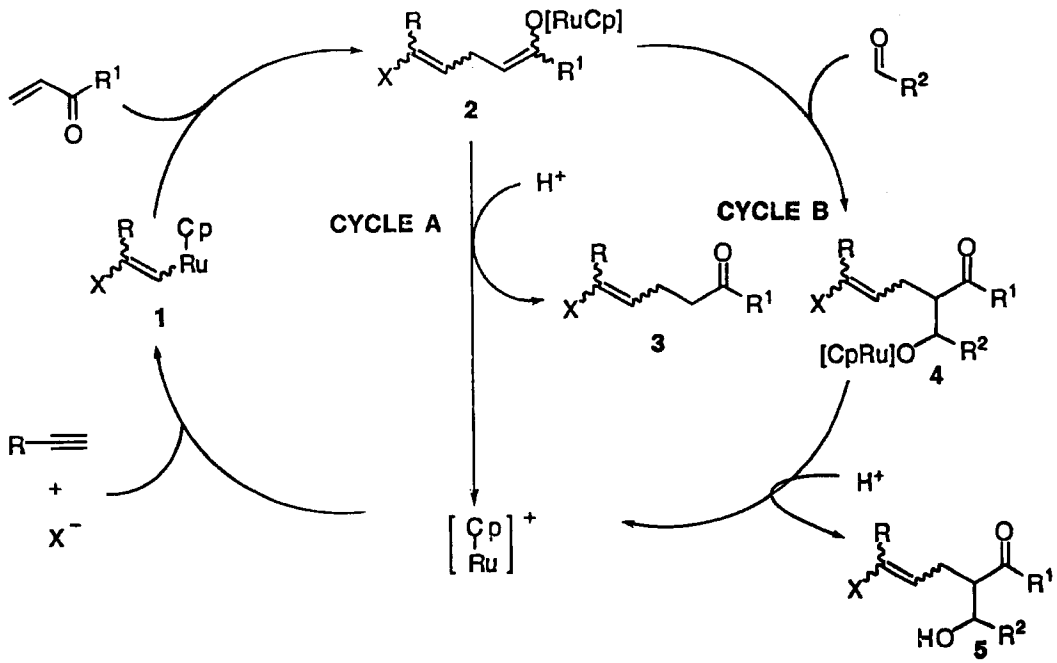
Trost, B. M.; *et al. Org. Lett.* **2000**, *2*, 1601
Trost, B. M.; *et al. J. Org. Chem.* **2001**, *66*, 7714

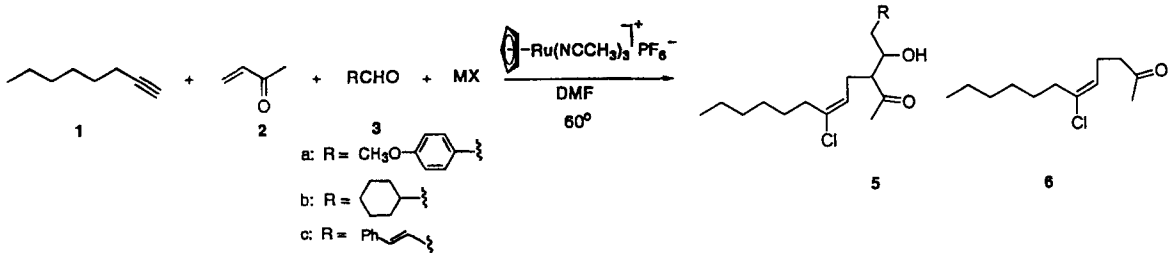
Four-Component Reaction





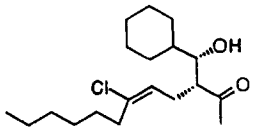
Trost, B. M.; *et al. J. Am. Chem. Soc.* **2000**, *122*, 8081.

Four-Component Reaction

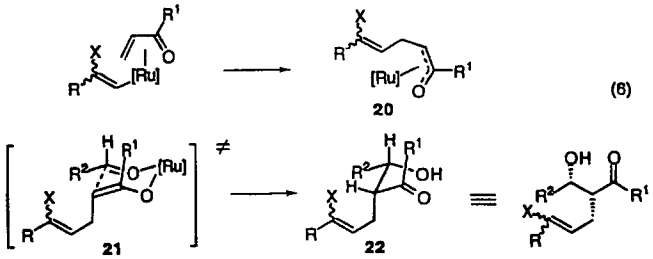


reaction condition	5	6
3.0 equiv aldehyde (**3a**)		
$(CH_3)_4NCl$ (3.0 equiv), $SnCl_4/5H_2O$ (15 mol%), 10 mol% Ru,	54% E/Z = 8.6/1 dr > 10/1	19%
Et_4NCl (3.0 equiv), $SnCl_4/5H_2O$ (15 mol%), 10 mol% Ru,	**5/6** = 2/1	
$(CH_3)_4NCl$ (3.0 equiv), $SnCl_4$ (15 mol%), 10 mol% Ru,	39% E/Z = 1/3.6	15%
$(CH_3)_4NCl$ (3.0 equiv), $SnCl_4/5H_2O$ (15 mol%), 10 mol% Ru, molecule sieve	15%	10%
6.0 equiv aldehyde (**3a**)		
$(CH_3)_4NCl$ (3.0 equiv), $SnCl_4/5H_2O$ (15 mol%), 10 mol% Ru,	62%	13%
3.0 equiv aldehyde (**3b**)		
$(CH_3)_4NCl$ (3.0 equiv), $SnCl_4/5H_2O$ (15 mol%), 10 mol% Ru,	51% E/Z = 8/1 dr > 10/1	23%

Structure of **5b**



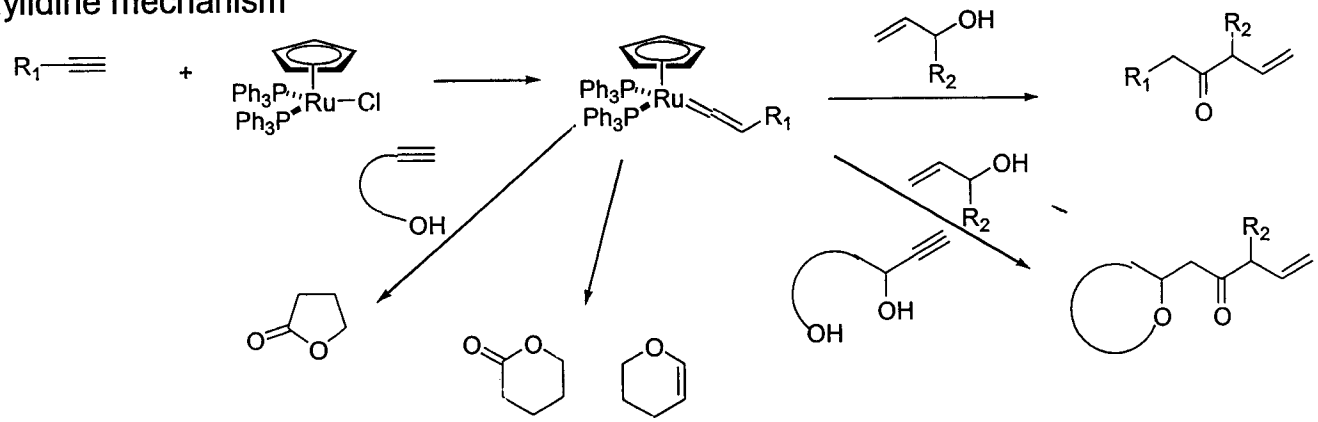
17



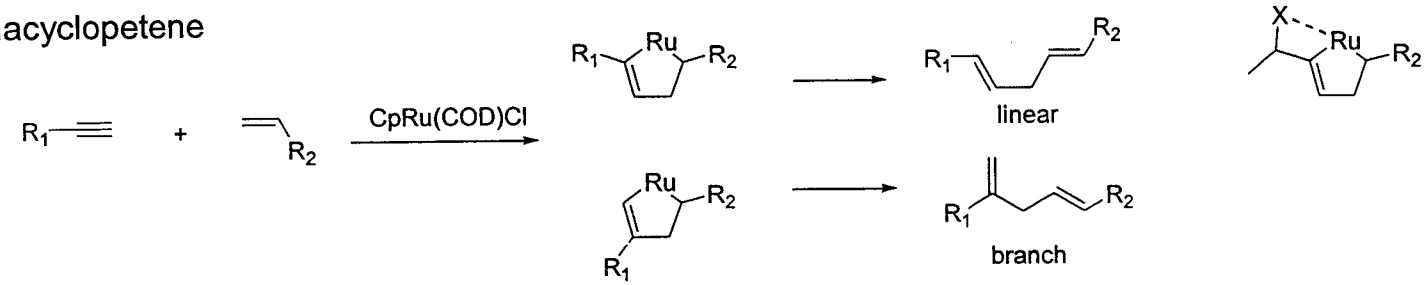
Trost, B. M.; *et al. J. Am. Chem. Soc.* **2000**, *122*, 8081.

Summary: the "Invention" of Reactions

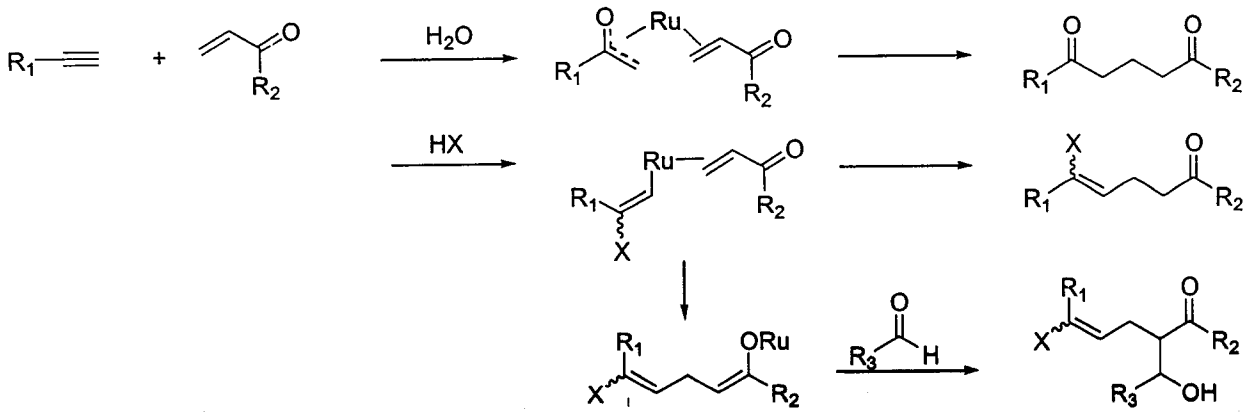
vinylidine mechanism



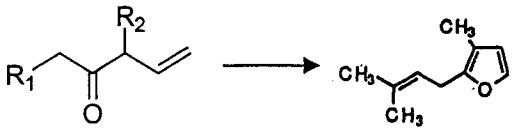
ruthenacyclopetene



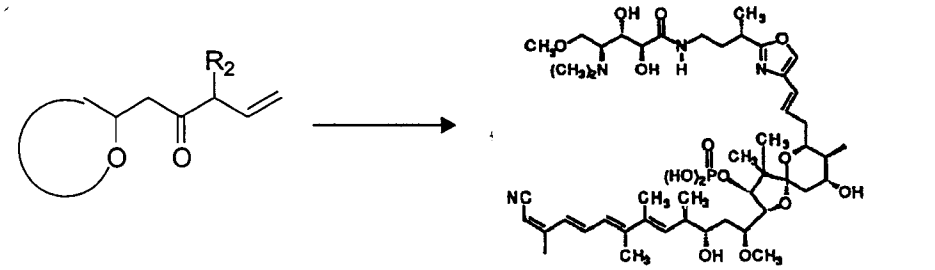
multicomponet reactions



The Application in Synthesis

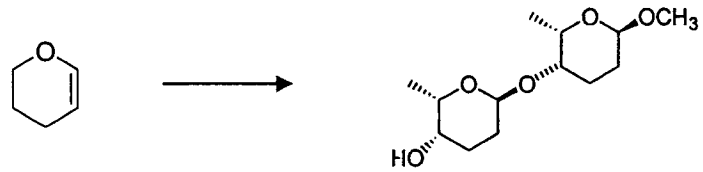


Rosefuran

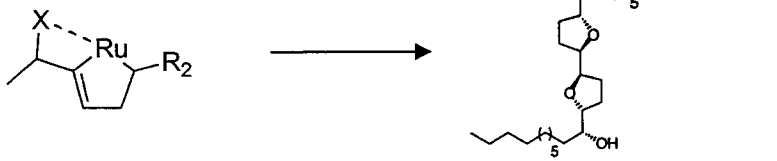


Calyculin

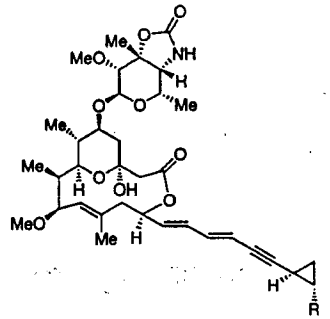
muricatacin



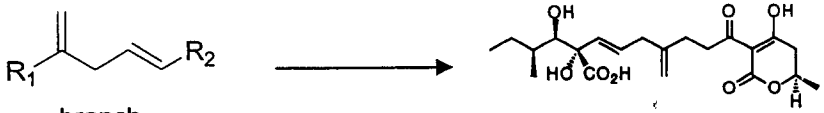
Narbosine B



Parviflorin

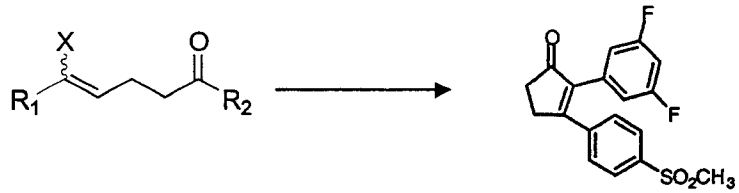


Deschlorocallipeltoside A



branch

Alternaric acid



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Trost, B. M.; Toste, F. D.; Pinkerton A. B. *Chem. Rev.* **2001**, *101*, 2067.
Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, asap.
Trost, B. M. *Science* **1991**, *254*, 1471.