Literature Seminar 6

04/03/17 Hiroyuki USUDA

Synthesis of Medium-Sized Rings

Cycloaddition approach

Contents

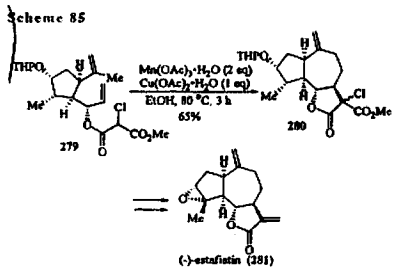
- Introduction – cyclization vs. cycloaddition
- Rh catalyzed cycloaddition
- π-complex and carbene complex
- recent interesting topics of [4+3]cycloaddition

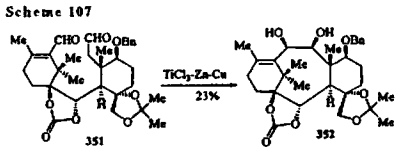
Introduction

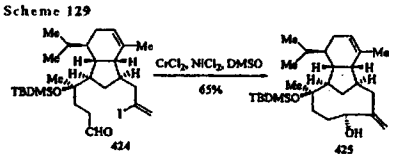
cyclization vs. cycloaddition

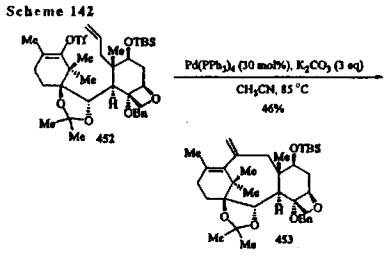
-natural product synthesis, combinatorial approach, how to get substrate, etc.

cyclization : RCM, radical cyclization, McMurry coupling, NHK reaction, Heck reaction, etc.









Chem Rev 100, 2963, (2000)

Rh catalyzed cycloaddition

1. Wender's group

1-1 intramolecular [5+2]

JACS 117, 4720-4721 (1995)

alkynes + vinylcyclopropane

↳ strain-driven cleavage

• ▷ & ▷// +C1 unit

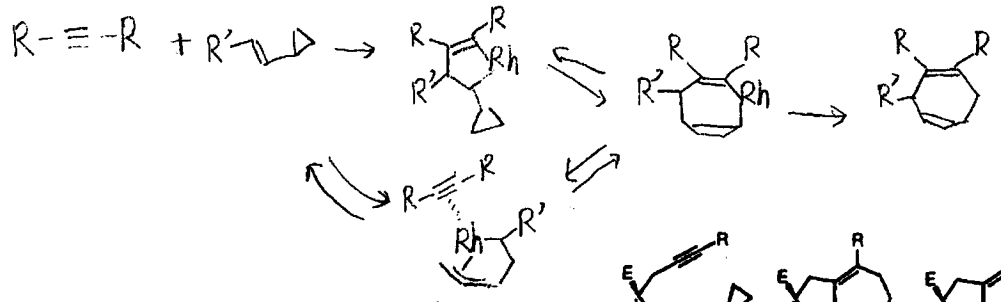
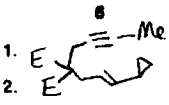


Table 1. Transition Metal Catalyzed Intramolecular [5 + 2] Cycloadditions of Vinylcyclopropanes and Alkynes

	Vinylcyclopropane-Alkyne	Cycloadduct(s), Yield	Reaction Conditions, time
	6	7	
1.		83%	A[a], 20 min.
2.		84%	B[b], 2 d
	8	9	
3.	a: R=Me	88%	B[b], 1.5 h
4.	b: R=TMS	83%	B[b], 3.5 h
5.	c: $R=CO_2Me$	74%	B[b], 1.25 h
6.	d: R=Ph	80%	B[b], 1.5 h
7.	e: R=H	50%[f]	C[c], 1.5 h

steric & electronic effect insensitive

		10	11	12	
8.	a: R=Me	89% (11:12=3.5:1)			B[b], 2 d
9.	a: R=Me	92% (11:12=1:2)			D[d], 2.5 h
10.	b: R=H	82% (only 11)			B[b], 2d
11.	c: $R=CO_2Me$	81% (only 11)			B[b], 16 h
12.	d: R=TMS	71% (only 12)			B[b], 7 d
		13	14		
13.		82%			D[d], 30 min

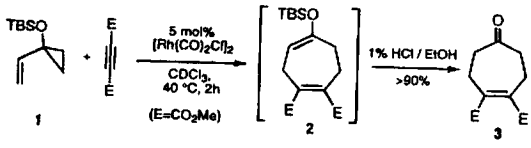
Wilkinson's cat

[a] A = 0.5 mol % $RhCl(PPh_3)_3$, 0.5 mol % AgOTf, PhMe, 110 °C. [b] B = 10 mol % $RhCl(PPh_3)_3$, PhMe, 110 °C. [c] C = 10 mol % $RhCl(PPh_3)_3$, THF, 100 °C. [d] D = 10 mol % $RhCl(PPh_3)_3$, 10 mol % AgOTf, PhMe, 110 °C. [e] E = CO_2Me. [f] Lower yield in this case due to product volatility.

- Wilkinson's cat in tolu: slow (2 d at 110°C) ~10 mol%
- ↳ in TFE: faster (19h at 55°C) Polarity favor formation of cationic Rh(I)
- ↳ +$AgOTf$ in tolu & much faster (20min at 110°C, 0.5 mol%)

1-2 intermolecular [5+2] -1 JACS 120, 10976 (1998), OL 2, 1609 (2000)

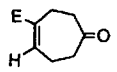
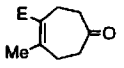
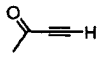
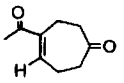
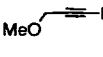
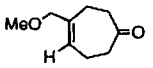
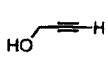
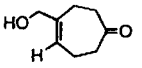
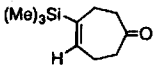
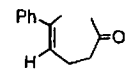
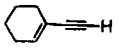
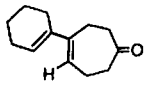
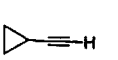
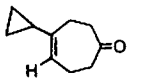
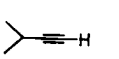
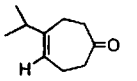
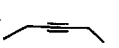
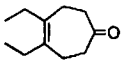
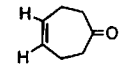
- -≡- + ▷ —Wilkinson's cat, +/-AgOTf→ no rxn or alkyne cyclotrimerized vinylcyclopropane isomerization
- OTBS ▷ is 5-10 folds more reactive than ▷
- $[Rh(CO)_2Cl]_2$ more reactive than Wilkinson's cat



1 2 3

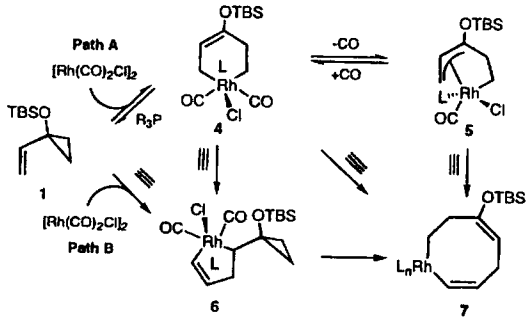
2/12

Table 1. The Transition Metal-Cata...ed [5+2] Cycloadditions of 1-(*tert*-Butyldimethylsilyloxy)-1-vinylcyclopropane with Alkynes

entry	alkyne[a]	product	time/ temperature[b]	yield[c]
1	E—≡—H		2h / 40 °C	93%
2	E—≡—Me		1.5h / 40 °C	92%
3			2.5h / 40 °C	88%
4			1.5h / 40 °C	88%
5			1.5h / 40 °C	74%
6	$(Me)_3Si$—≡—H		2h / 40 °C	77%
7	Ph—≡—H		3h / 30 °C	81%
8			3h / 40 °C	75%
9			2h / 40 °C	88%
10			2.5h / 40 °C	84%
11			7h / 40 °C	65%
12	H—≡—H		6h / 40 °C	79%

[a] E = CO_2Me. [b] See General Procedure in footnote 16. [c] Overall yields for cycloaddition and hydrolysis steps.

Scheme 1



← proposed mechanism

1 + 50mol% $[Rh(CO)_2Cl]_2$

↓

NMR showed the mixture of 4 + 5.

↓ + ≡

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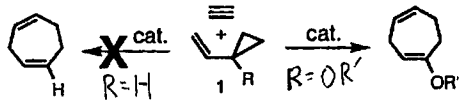
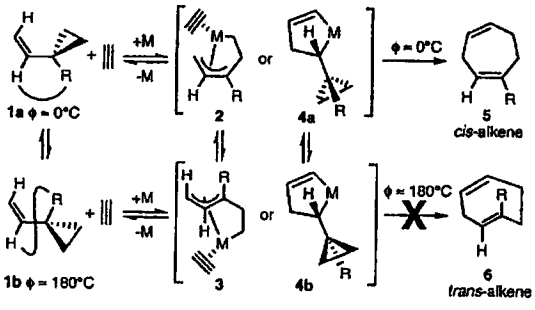
1-3 intermolecular [5+2] - simple VCP JACS 123, 179(2001)



contrasting reactivity { ◦ electronic contribution of heteroatom ◦ conformational influence



S-cis

vs

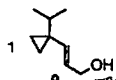
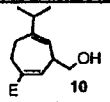
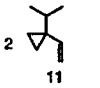
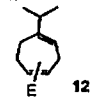
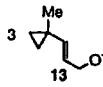
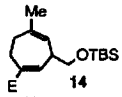
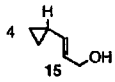
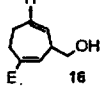
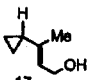
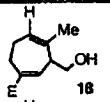
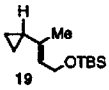
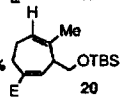
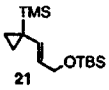
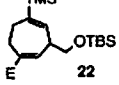
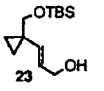
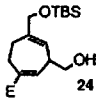
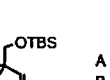
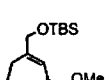
S-trans

→ R = bulky substituent, rxn proceeds ? → table 2

ent 1 vs 3 vs 4 : iPr > Me > H !!

TMS ⤴ surrogate

Table 2. Substituent Effects on the [5+2] Cycloadditions with Methyl Propiolate (E = CO_2Me)

Entry	VCP	Cond.[a]/ Yield	Product
1	 9	A 2h/ 82% (OTBS A 2h/93%)	 10
2	 11	A 1.5h/ 76%	 12
3	 13	A 8h/ 81%	 14
4	 15	A 30h/ 23% B 2h/ dec.	 16
5	 17	A 72h/ 38% B 6h/ dec.	 18
6	 19	A 72h/ 64% B 45 min/ 69%	 20
7	 21	A 3h/ 53%	 22
8	 23	A 2h/ 82%	 24
9	 25	A 20h/ 75% B 3h/ 76%	 26
10	27	A 15h/ 63% d.r. = 2:1	28
11	29	A >24 h/ no rxn B 21h/ 62% d.r. = 1:1	30

[a] Conditions: A = 5 mol % $[Rh(CO)_2Cl]_2$, DCE, 80 °C; B = 5 mol % $[Rh(CO)_2Cl]_2$, 5% TFE in DCE, 80 °C.

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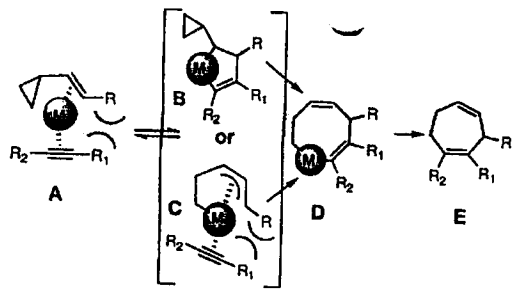


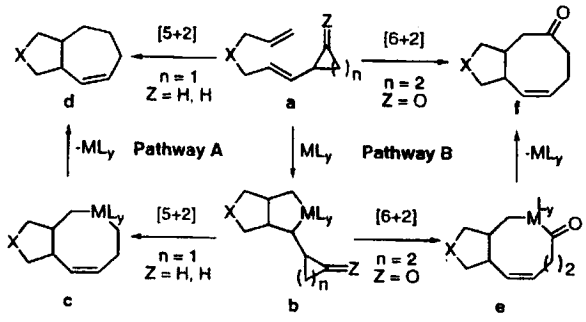
High regioselectivity is consistent with minimization of steric effects during C-C bond formation

↘ R-≡-H only R-≡-R' not reported (R'≠H)

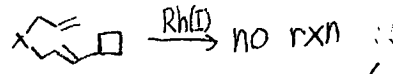
R = CO_2Me, Ph, CH_2OMe, CH_2OH, C_3H_7, TMS

1-4 : intramolecular [6+2] JACS 122, 7815 (2000)

Scheme 1



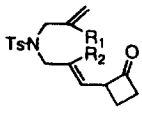
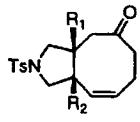
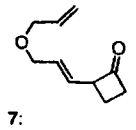
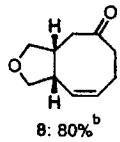
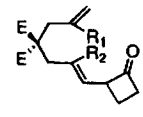
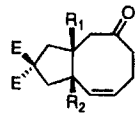
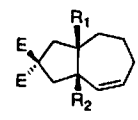
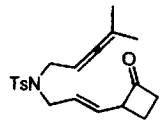
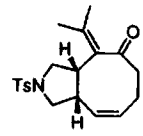
replacement of cyclopropane to cyclobutane



Rh(I) → no rxn : is less reactive

↙ modulation by heteroatom

Table 2. Rh(I)-Catalyzed [6+2] Cycloaddition Reactions of 2-Vinylcyclobutanone Substrates[a]

2-Vinylcyclobutanone Substrates	Cycloadducts, Yield [a]	Reaction Conditions,[c] Time
		
1: R_1=R_2=H	2: 95%	A, 3h
3: R_1=H, R_2=Me	4: 78%	B, 20h
5: R_1=Me, R_2=H	6: 71%	C, 26h
		
7:	8: 80%[b]	C, 14h
		
9: R_1=R_2=H	10a: 80% (cis) [10b: 6% (trans)]	10c: 8% C, 17h
11: R_1=H, R_2=Me	12a: 77%	12b: 17% D, 20h
13: R_1=Me, R_2=H	14: 78%	C, 26h
		
15:	16: 91%	E, 0.75h

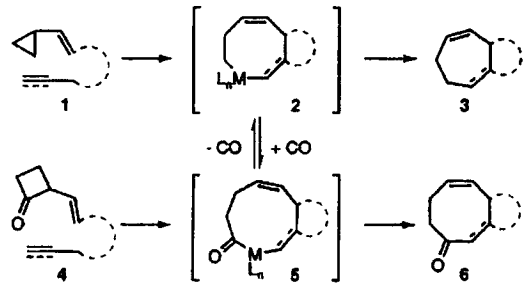
[a] Isolated yield unless otherwise indicated. [b] Isolated yield as its dinitrophenyl hydrazone derivative. [c] A = 10 mol % $RhCl(PPh_3)_3$, 10 mol % AgOTf, PhMe (0.014 M), 110 °C. B = 10 mol % $RhCl(CO)(PPh_3)_2$, 10 mol % AgOTf, PhMe (0.014 M), 110 °C. C = 5 mol % $[Rh(CO)_2Cl]_2$, 10 mol % P(*n*-Bu)$_3$, 10 mol % AgOTf, PhMe (0.014 M), 110 °C. D = 5 mol % $[Rh(CO)_2Cl]_2$, 10 mol % P(*n*-Bu)$_3$, 10 mol % AgOTf, PhMe (0.010 M), 110 °C. E = 5 mol % $[Rh(CO)_2Cl]_2$, PhMe (0.010 M), 110 °C. [d] E = CO_2Me; Ts = *p*-$CH_3C_6H_4SO_2$.

- Rh catalyzed isomerization is not observed
- byproduct 10c, 12d : decarbonylation, an atmosphere of CO were not successful

↓ New reaction

1-5 : [5+2+1] cycloaddition JACS 124, 2876 (2002)

Scheme 1



1 → 2 → 3 : [5+2]

4 → 5 → 6 : [6+2]

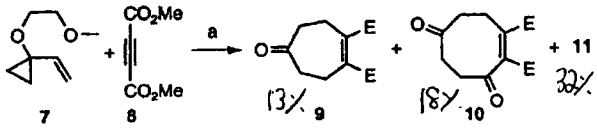
4 → 5 → 2 → 3 : [6+2-1] (undesired product of [6+2])

↓

1 → 2 → 5 → 6 : [5+2+1]

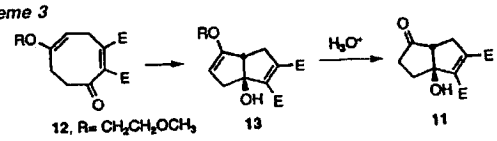
↓ isomerization of 12 → 11 ([3,3,0])

Scheme 2[a]



[a] Key: (a) CO (1 atm), $[Rh(CO)_2Cl]_2$ (5 mol %), 1,2-dichloroethane (0.1M, 7), 60 °C; H_3O^+.

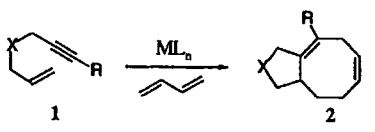
Scheme 3



4/12

2. Rh catalyzed [4+2+2] process

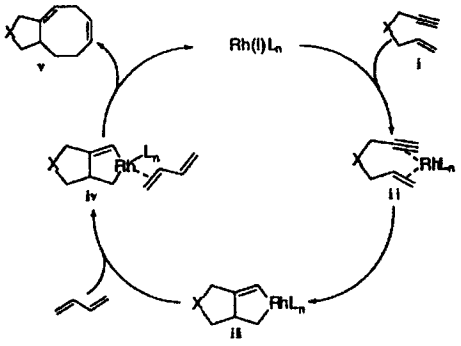
2-1 P.A. Evans JACS 124, 8782 (2002)



(1)

Ni(0) catalyzed intermolecular [4+4] cycloisomerization & intramolecular heterocycloaddition are well-known, while there is a significant limitation due to the poor selectivity in heterocycloadditions employing stereoelectronically different 1,3-butadiene derivatives.

Scheme 1



to suppress the formation of homocycloaddition or oligomerization

→ electronic difference between enyne and diene?

↓

result (Wilkinson's cat)

ent1. homocyclization

(+AgOTf) ent2. excellent selectivity, least amt of oligomer

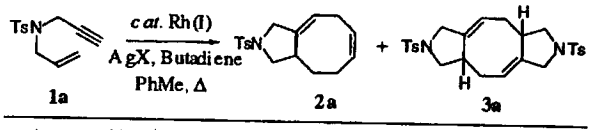
(+AgSbF$_6$) ent5. homodimer

due to oligomerization of butadiene

↓

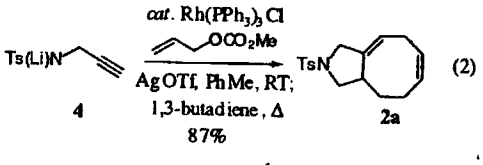
results low concentration of butadiene.

Table 1. Development of the Rhodium-Catalyzed [4 + 2 + 2] Cycloaddition Reaction



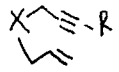
entry	additive[a,b]	ratio of 2a:3a[c]	yield of 2a (%)[d,e]	yield of 3a (%)[f]
1	none	1:8	7 (0)	57
2	*AgOTf*	*28:1*	*85 (4)*	*3*
3	$AgBF_4$	11:1	74 (0)	7
4	$AgPF_6$	2:1	49 (2)	27
5	*$AgSbF_6$*	*1:44*	*2 (6)*	*89*

[a] All reactions were carried out on a 0.5 mmol reaction scale using 10 mol % of Wilkinson's catalyst [$Rh(PPh_3)_3Cl$] in refluxing toluene under an atmosphere of 1,3-butadiene. [b] The rhodium catalyst was *modified* with 20 mol % of the silver salt as indicated. [c] Ratios of *hetero-* and *homo-*cycloaddition products were determined by capillary GLC and HPLC on aliquots of the crude reaction mixture. [d] GLC yields. [e] Yields in parentheses are for cyclooctadiene (by GLC). [f] HPLC yields.



(2)

one-pot reaction



↓ results low concentration of butadiene.

Table 2. Scope of the *Inter*molecular Rhodium-Catalyzed [4 + 2 + 2] Cycloaddition Reaction (eq 1)[a]

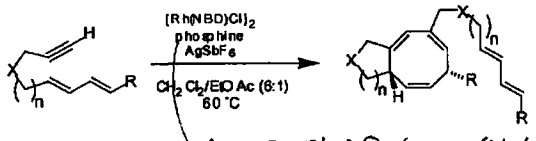
entry	X	R		ratio of 2:3[b]	yield of 2 (%)[c]
1	TsN	H	a	≥19:1	91
2	"	Me	b	≥19:1	91
3	"	Ph	c	≥19:1	87
4	SO_2	H	d	≥19:1	79
5	"	Me	e	≥19:1	73
6	"	Ph	f	≥19:1	87
7	O	H	g	≥19:1	71
8	"	Me	h	≥19:1	81
9	"	Ph	i	≥19:1	92

[a] All reactions were carried out on a 0.5 mmol reaction scale using 10 mol % of Wilkinson's catalyst [$Rh(PPh_3)_3Cl$], modified with 20 mol % AgOTf, in refluxing toluene under an atmosphere of 1,3-butadiene. [b] Ratios of *hetero-* and *homo*cycloadducts were determined by 400 MHz ^1H NMR with the exception of **2a/3a** (26:1 by crude GLC/HPLC). [c] Isolated yields.

tolerant of both alkynes.

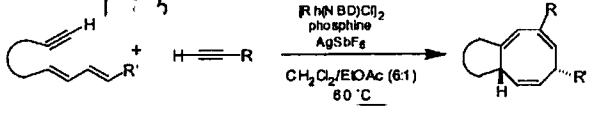
2-2 Gilbertson JACS 124, 8784 (2002)

Table 1. Dimer Formation[a]



Me-DuPHOS (upto 41% ee)

Table 2. [4 + 2 + 2] Cyclization with Incorporation of a Second Alkyne

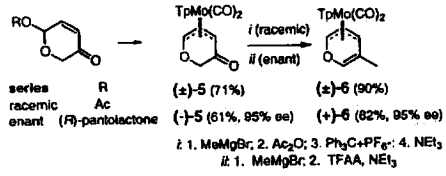


π-complex- and carbene complex-

1. Liebeskind's group

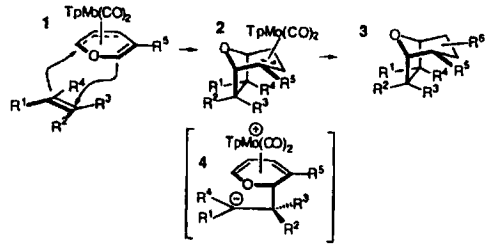
1-1. [5+2] cycloaddition JACS 121, 5811 (1999) OL 2, 3909 (2000) OL 2, 4083 (2000)

Scheme 2. Synthesis of $TpMo(CO)_2$(3-methyl-η-4,5,6-pyranyl)



- enantiopure Mo-π complexs are easily obtained.
- sufficiently air and moisture stable
- synthetically potent enantiomerically pure scaffolds for asymmetric construction

Scheme 1

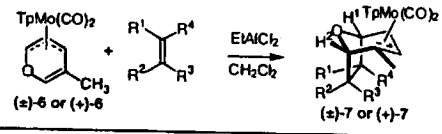


stepwise cycloaddition with electron deficient alkenes (via 4)

2 → 3 demetallation / functionalization

Tp = hydridotrispyrazolylborato

Table 1. [5 + 2] Cycloaddition of η^3-Pyranylmolybdenum Complexes



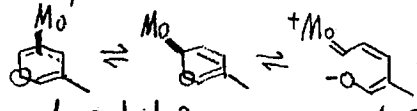
entry	alkene	cndns[a]	yld, exo:endo	prdt	R^1	R^2	R^3	R^4	%ee[b]
1	CH_2=CHCHO	20%, rt 2.5 h	87%, 10:1	*exo*-**7a**	HCO	H	H	H	
				endo-**7a**	H	H	H	CHO	
2	CH_2=CHCOMe	10%, rt 1.5 h	94%, 8.4:1	*exo*-**7b**	MeCO	H	H	H	
				endo-**7b**	H	H	H	COMe	
3	CH_2=CHCO$_2$Me	20%, rt 5 h	88%, 3.5:1	*exo*-**7c**	MeO$_2$C	H	H	H	95%
				endo-**7c**	H	H	H	CO$_2$Me	95%
4	2-cyclohexenone	20%, rt 4 h	93%, 1:0	*exo*-**7d**	−CO(CH$_2$)$_3$−		H	H	96%
				endo-**7d**	H	H	−(CH$_2$)$_3$CO−		
5	CH_2=CHCN (6 equiv)	120%, rt 4.5 h	57%, 0.64:1	*exo*-**7e**	NC	H	H	H	23%
				endo-**7e**	H	H	H	CN	23%
6	*N*-methylmaleimide	110%, rt 10 min	99%, 8:1	*exo*-**7f**	−CON(Me)CO−		H	H	97%
				endo-**7f**	H	H	−CON(Me)CO−		>90% ee[c]
7	(*E*)-2-PhCHCH(Me)CHO	20%, rt 4 h	91%, 1:1.2	*exo*-**7g**	HCO	Ph	H	Me	
				endo-**7g**	Me	Ph	H	CHO	
8	PhCH=C(CN)$_2$	20%, rt 3 h	96%, 1:0	*exo*-**7h**	NC	Ph	H	CN	
				endo-**7h**	NC	H	Ph	CN	
9	DMAD	110%, rt 10 min	43%, - - - -	**7i**	EtO$_2$C	CO$_2$Et	C−C bond		

[a] Mol % $EtAlCl_2$, temp, time. [b] Enantiomeric excess of product prepared from (+)-**6** of 97% ee. [c] Small amount of impurity precluded an accurate determination of the minor isomer ee. However, recrystallization of *endo*-**7f** gave product in >99% ee.

6 + electron deficient olefin + $EtAlCl_2$ (0-120 m, 1/1) rt

ee → racemization is not so problematic (ent 3, 4, 6)

ent. 5 → least reactive alkene, slow racemization of (+)-6 in the presence of $EtAlCl_2$



→ racemization ?

ent. 7 exo : endo = 1 : 1.2, pure endo-7i $\xrightarrow[CH_2Cl_2]{EtAlCl_2}$ exo : endo = 1 : 1.2

→ support the formation of intermediate 4 ?

demetallation

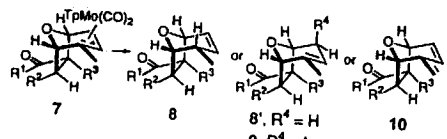


Figure 1.

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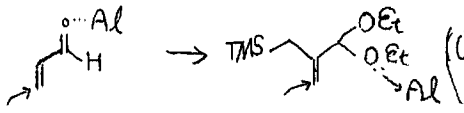
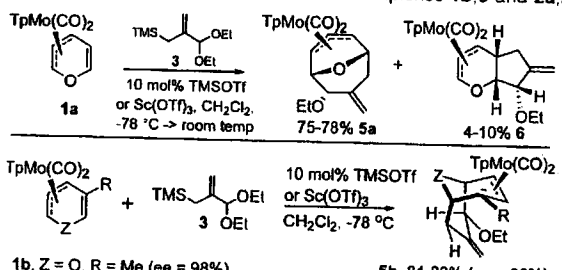
1-2 [5+3] cycloaddition JACS 125, 9026(2003)

C-2 unit → [4+3]

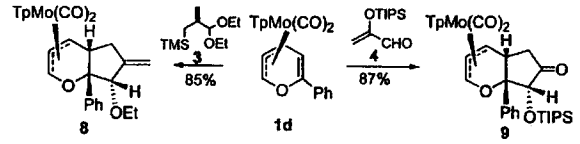
C-3 unit → [5+3] → [3.3.1] cyclooctenes (Oxyallyl cation precursor)



Scheme 1. [5+3] Cycloadditions of **3** to Complexes **1b,c** and **2a,b**

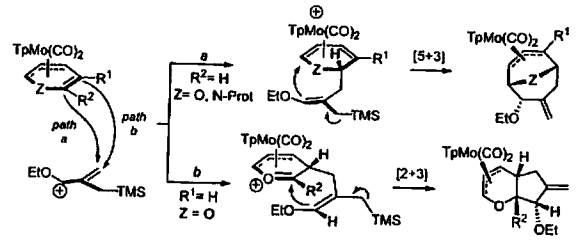


Scheme 2. [2+3] Cycloadditions of **3** and **4** to Complex **1d**[a]



[a] Conditions: 10 mol % $Sc(OTf)_3$, CH_2Cl_2, −78 °C, 2 h.

Scheme 3. Proposed Mo- and O-Promoted Stepwise Mechanisms



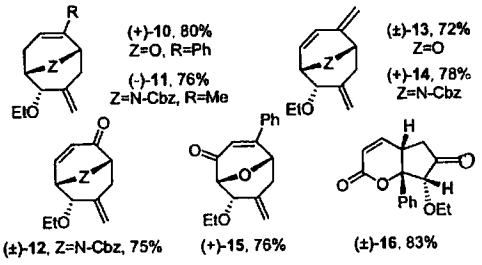
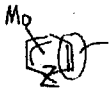


Figure 2. Demetalation products from [5+3] and [2+3] cycloadducts. Enantiomeric excess >99.5% for (+)-**10** and (+)-**15** was determined by HPLC analysis. Similar ee's are presumed for (+)-**14** and (−)-**11**.

from 3-substituted π-complex → [5+3]
- facial diastereoselectivity: opposite Mo site
- endo selectivity
- without racemization

from 2-substituted π-complex → [2+3]!
- opposite regiochemistry
(the alkoxy group appears adjacent to 2-phenyl substituent)

two different stepwise mechanism,

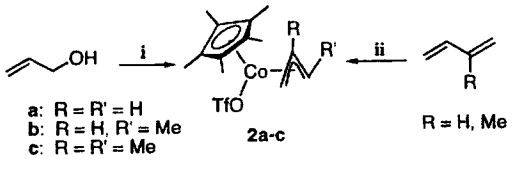


- uniquely nucleophilic by the cation stabilizing ability of the adjacent η^3-allyl Mo moiety

R^2=H : [5+3] : Mo-promoted path

R'=H (Z=O) : [2+3] : Nonbonded steric effects from the Phenyl group at C-2 retard the Mo-promoted path a and make more favorable the O-promoted mechanism

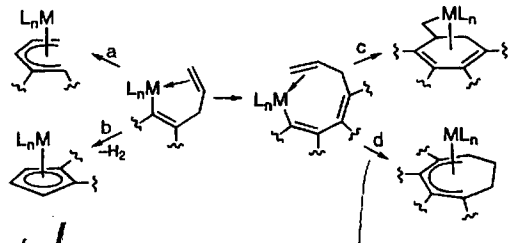
2. Allyl/Alkyne [3+2+2] cycloaddition Stryker et al JACS 120, 9702(1998) JACS 121, 10640(1999)



(1)

Conditions: i. $(C_5Me_5)Co(C_2H_4)_2$ (**1**), TfOH, Et_2O, -78 °C→RT, 4h
ii. $(C_5Me_5)Co(C_2H_4)_2$ (**1**), hexane, 65 °C, 4-12h; then step i.

Scheme 1



Path a~c has been already reported

2x ≡

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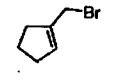
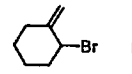
Table 1. [3 + 2 + 2] Allyl/Alkyne Cycloa...n[a]

Entry	Allyl complex/ precursor	Alkyne	Product	Yield[b]
1	2a	H—≡—H	3a (R, R' = H)	52 (66)
2	2b	H—≡—H	3b (R = H, R' = Me)	79 (85)
3	2c	H—≡—H	3c (R, R' = Me)	80
4	2a	Ph—≡—H	3d	59
5	2a	tBu—≡—H	3e	88
6[c]		H—≡—H	3f (n = 1)	47
7[c]		H—≡—H	3g (n = 2, BF_4 salt)	59

[a]Conditions: CH_2Cl_2, excess alkyne (PhC≡CH, 3 equiv; tBuC≡CH, 10 equiv), -78 °C→RT, 12h. [b]Yield of spectroscopically homogeneous material obtained from chromatography. Yields in parenthesis are overall yields obtained from complex 1, without isolation of the allyl triflate complex 2. [c]Conditions: i. $(C_5Me_5)Co(C_2H_4)_2$ (1), THF, 0 °C→RT 6h; ii. AgOTf or $AgBF_4$, HC≡CH, acetone, RT, 0.5h.

in THF: path b : dehydrogenative [3+2]

↓

CH_2Cl_2 : path d

· endo selective

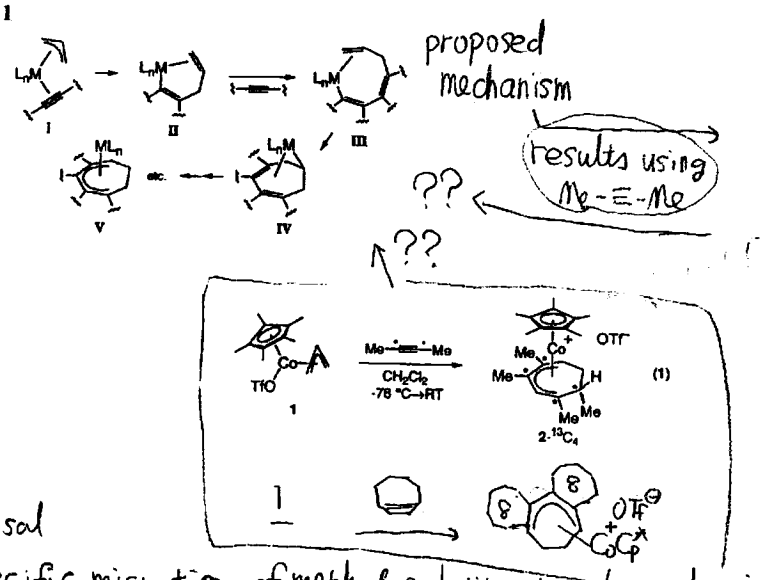
Table 2. Synthesis of Functionalized Cycloheptadienes

Cyclo-adduct	Diene complex[a]	Yield[b]	Free Diene[c]	Yield[d]
3a	4a (R, R' = H)	71	5a (R, R' = H)	67
3b	4b (R = H, R' = Me)	63	5b (R = H, R' = Me)	62
3c	4c (R, R' = Me)	89	5c (R, R' = Me)	49
3d	4d	72	5d	50
3g	4g	96	5g	62

[a]Conditions: $NaCH(CO_2Me)_2$, THF, RT, 4h. [b]Yield of spectroscopically homogeneous material obtained from pentane extraction under N_2 and used without further purification. [c]Conditions: $[(C_5H_5)_2Fe]^+PF_6^-$ (2.5 equiv), CH_3CN/pentane, -35 °C→RT, 5-10 min. [d]Yield is of isolated pure material obtained from flash chromatography.

mechanism?

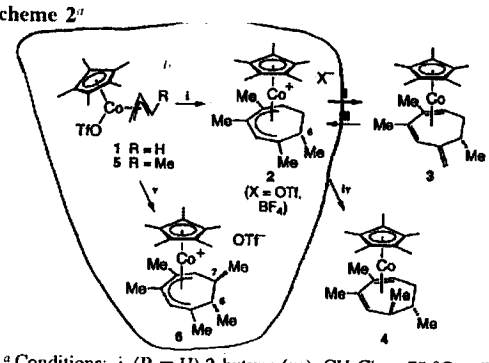
Scheme 1



proposal

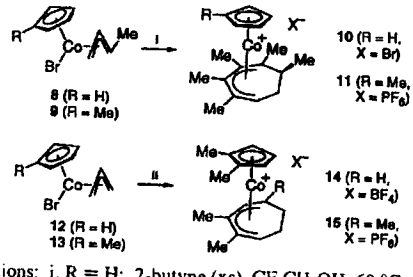
(· specific migration of methyl substituents along the ring periphery ??
· skeletal reorganization of the carbon frame work

Scheme 2[a]



[a] Conditions: i. (R = H) 2-butyne (xs), CH_2Cl_2, −78 °C → RT, 12 h, 81%; ii. NaH, THF, RT, 10h, 77%; iii. $HBF_4 \cdot Et_2O$, Et_2O, RT, 99%; iv. $LiEt_3BH$, THF, −78 °C → RT, 10 h, 53%; v. (R = Me) 2-butyne (xs), CF_3CH_2OH, 55 °C, 7 h, 78%.

Scheme 3[a]



[a] Conditions: i. R = H: 2-butyne (xs), CF_3CH_2OH, 60 °C, 12 h, 54%; R = Me: same as for R = H, but followed by KPF_6, H_2O, 39%. ii. R = H: 2-butyne (xs), $AgBF_4$, acetone, −78 °C → RT, 12 h, 6%; R = Me: 2-butyne (xs), CF_3CH_2OH, 55 °C, 7h; then KPF_6, 43%.

8, 9 → 10, 11 : straightforward delivery

12, 13 → 14, 15 : ???

i) cyclization of the vinyl olefin intermediate (II) can be faster than incorporation of the second alkyne

ii) electrophilic Co(III) is capable of activating C-C bond in coordinative five-membered ring under very mild conditions

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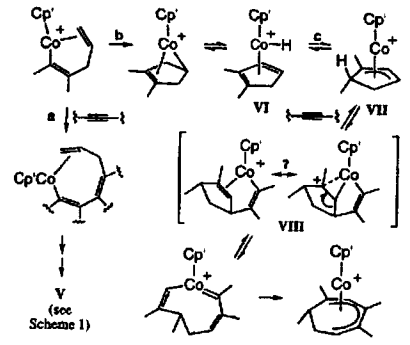
proposed mechanism.

Scheme 4

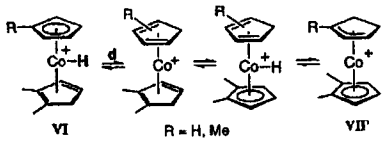


Reactivity of alkyne, allyl, Cp decides the pathway

cf. terminal alkyne · path a

← selective cleavage of the less substituted Cp ring

Scheme 5



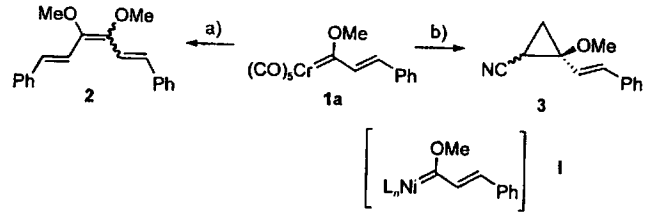
equilibrium between VII and VII'

3. Fischer carbene cycloaddition – transmetallation to Ni

Barluenga et al. Angew 42, 3008 (2003)

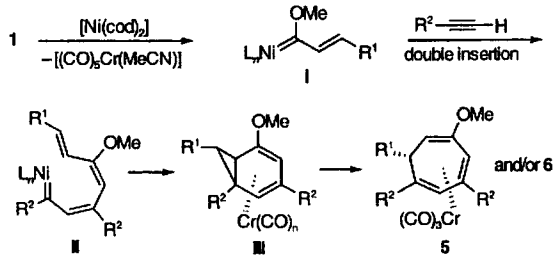
Ni carbene complex mediated rxns

application to Dötz-type reaction



Scheme 1. Ni^0-catalyzed dimerization and cyclopropanation of chromium carbene complex **1a**. Reagents and conditions: a) $[Ni(cod)_2]$ (10 mol%), THF, 25 °C, 2 h, 90%; b) acrylonitrile, $[Ni(cod)_2]$ (10 mol%), MeCN, 25 °C, 3 h, 85%.

in the absence of Ni(0): no rxn



Scheme 2. Proposed mechanism for the formation of **5** and **6**.

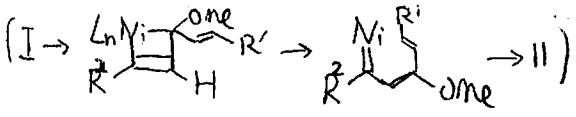
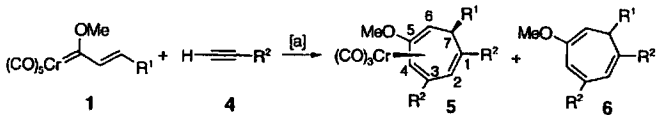


Table 1: [3+2+2] cyclization of chromium alkenyl carbene complexes **1** with alkynes **4**.

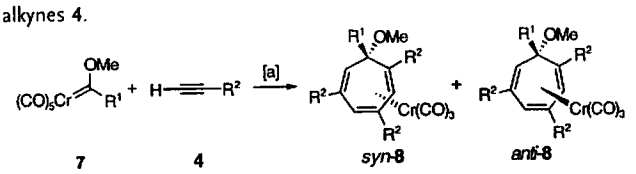


entry	R^1	R^2	5 [%][b]	6 [%][b]
1	Ph	*n*Pr	**5a** (86)	–
2	ferrocenyl	*n*Pr	**5b** (73)	–
3	2-furyl	*n*Pr	**5c** (76)	–
4	*n*Pr	*n*Pr	**5d** (62)	–
5	Ph	Me_3Si	**5e** (80)	–
6	Ph	$(CH_2)_3CN$	**5f** (78)	–
7	2-furyl	Ph	**5g** (30)	**6g** (40)
8	Ph	CO_2Me	–	**6h** (75)

[a] MeCN, **1**:[Ni(cod)$_2$] 1:3:1.1, −10 to 20 °C, 2 h. [b] Yields of isolated products.

Mechanism

Table 2: [2+2+2+1] cyclization of chromium carbene complexes **7** with alkynes **4**.



entry	R^1	R^2	8 [%][b]	*syn*:*anti*[c]
1	Me	*n*Pr	**8a** (92)	>98:2
2	Me	Me_3Si	**8b** (65)	>98:2
3	Me	$(CH_2)_3CN$	**8c** (96)	>98:2
4	c-C_3H_5	*n*Pr	**8d** (75)	>98:2
5	*p*-$MeOC_6H_4$	*n*Pr	**8e** (83)	>98:2
6	2-furyl	*n*Pr	**8f** (86)	90:10
7	Ph	*n*Pr	**8g** (68)	60:40

[a] MeCN, **7**:**4**:[Ni(cod)$_2$] 1:4:1.1, −10 to 20 °C, 2 h. [b] Yields of isolated products. [c] ^{1}H NMR spectroscopy (300 MHz) on the crude reaction mixture.

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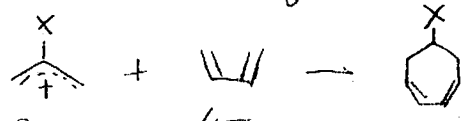
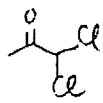
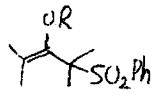
Recent Interesting Topics of [4+3] Cycloaddition

<general>  Diels-Alder type

2π 4π 7-membered ring

4π :  ,  >> acyclic butadiene

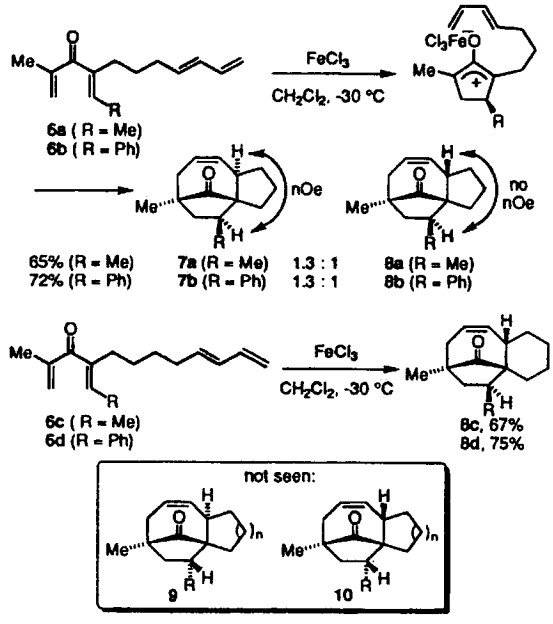
2π :  ,  etc +Lewis acid

intramolecular > intermolecular - need for rapid capture of short-lived reactive intermediates

1. Nazarov → [4+3] West et al. JACS 121, 876(1999), OL 5, 2747(2003)

- intramolecular

Scheme 2



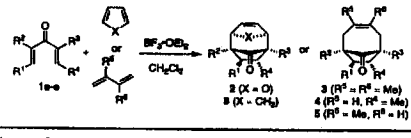
FeCl3 : 1eq or 0.2eq

diastereoselectivity

- preferred approach from the less hindered face of the cyclic oxyallyl cation
- modest endo-exo selectivity (6a, 6b)
- complete exo selectivity (6c, 6d)
  - unfavorable interactions between the diene unit and the tether?

- intermolecular

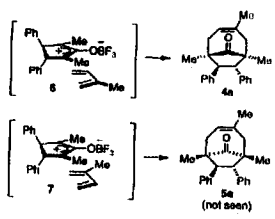
Table 1. Domino Nazarov/Intermolecular [4 + 3]-Cycloaddition Reactions of Dienones with Simple Dienes[a]



entry	dienone	R^1	R^2	R^3	R^4	1,3-diene[b]	X	R^3	R^5	temperature/time	products (% yield)[c]
1	1a	Ph	Me	Me	Ph	furan	O			−78 °C/0.5 h	2a (70)
2	1a	Ph	Me	Me	Ph	DMB		Me	Me	−78 °C/3 h[d]	3a (50)
3	1a	Ph	Me	Me	Ph	isoprene		Me	H	−25 °C/2.5 h[d]	4a (20)
4	1b	Ph	Me	Me	H	furan	O			−50 °C/2 h	2b (71)
5	1b	Ph	Me	Me	H	C_5H_6	CH_2			−20 °C/2 h	8b (62)
6	1b	Ph	Me	Me	H	DMB		Me	Me	−20 °C/2 h	3b (91)
7	1b	Ph	Me	Me	H	isoprene		Me	H	−20 °C/2 h	4b + 5b (84; 5:1)[e]
8	1c	Et	Me	Me	H	furan	O			−50 °C/3 h	2c (72)[f]
9	1c	Et	Me	Me	H	C_5H_6	CH_2			−20 °C/2 h	8c (64)
10	1c	Et	Me	Me	H	DMB		Me	Me	−20 °C/2 h	3c (93)
11	1c	Et	Me	Me	H	isoprene		Me	H	−20 °C/2 h	4c + 5c (84; 4.2:1)[e]
12	1d	$(CH_2)_4$		Me	H	DMB		Me	Me	−20 °C/1.5 h	3d (92)
13	1e	$(CH_2)_5$		Me	H	DMB		Me	Me	40 °C/1 h[g]	3e (67)
14	1e	$(CH_2)_5$		Me	H	isoprene		Me	H	40 °C/1 h[g]	4e + 5e (55; 1.4:3)[e]

[a] Standard Procedure. To a solution of dienone 1 and 1,3-diene (2.0 equiv) in CH_2Cl_2 at −20 °C was added $BF_3{\cdot}OEt_2$ (1.0 equiv), and the reaction was maintained at that temperature for 2 h. Saturated aqueous $NaHCO_3$ was added, and the mixture was allowed to warm to room temperature. Following extraction of the aqueous phase with CH_2Cl_2, the combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated, and the resulting crude product was purified by flash chromatography. [b] Abbreviations: DMB = 2,3-dimethylbutadiene; C_5H_6 = cyclopentadiene. [c] Isolated yields after chromatography. [d] In entries 2 and 3, 10 equiv of diene was used. [e] Regioisomers 4 and 5 were isolated as an inseparable mixture and the ratios determined by integration of ^1H NMR signals. [f] Cycloadduct 2c was isolated as a 1.3:1 ratio of diastereomers epimeric at R^1. [g] Reactions carried out in $ClCH_2CH_2Cl$ using 0.1 equiv of $BF_3{\cdot}OEt_2$.

Scheme 2



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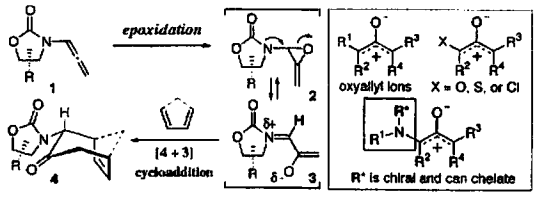
2 Epoxidation of allenes → [4+3] Hsung etal. JACS 123, 7174 (2001)
JACS 125, 12694 (2003)
Angew 43, 515 (2004)

concept

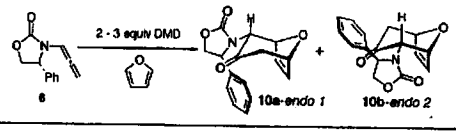
Scheme 1



allenamide 1 → chiral allene oxide 2
⇅
chiral nitrogen stabilized oxyallyl cation 3
→ [4+3]

results

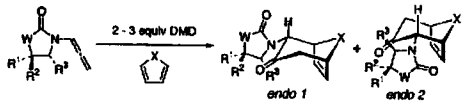
Table 1



entry	solvent[a]	temp,[b] °C	additive [2.0 equiv]	yield,[c] %	ratio of 10a:b[d]
1	CH_2Cl_2	−40	none	75	75:25
2	Et_2O	−40	none	77	75:25
3	CH_3CN	−40	none	<10	
4	THF	−40	none	80	75:25
5	THF	25	none	80	75:25
6	THF	−78	none	70	82:18
7	THF	−40	$LiClO_4$	81	75:25
8	THF	−40	$MgBr_2$	<10	
9	THF	25	$ZnCl_2$	40	90:10
10	THF	−40	$ZnCl_2$	77	94:6
11	THF	−78	$ZnCl_2$	80	≥96:4

[a] Reaction solvent indicates the solvent that the allenamide **6** and 10.0 equiv of furan were dissolved in, although DMD was generated and added as a solution in acetone. [b] Reactions took 30 min at room temperature, 5−10 h at −45 °C, and 10−20 h at −78 °C to complete. [c] All yields are isolated yields. [d] Ratios were determined by using ^1H and/or ^{13}C NMR.

Table 2

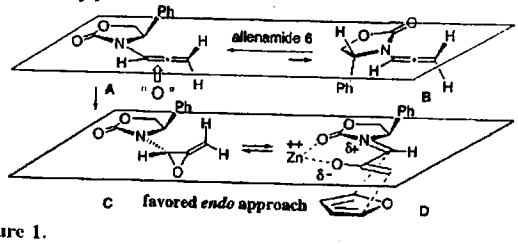


entry[a]	allenes	W	R^1	R^2	R^3	X	adducts	yields,[b] %	*endo* ratio[c]
1	6	O	H	H	Ph	CH_2	**11**	40	≥95:5
2	12	NMe	Me	H	Ph	O	**13**	60	≥95:5
3	12	NMe	Me	H	Ph	CH_2	**14**	83	≥96:4
4	15	O	H	H	Bn	O	**16**	67	77:23
5	17	O	H	H	$CHPh_2$	O	**18**	74	≥95:5
6	17	O	H	H	$CHPh_2$	CH_2	**19**	62	93:7
7	20	O	H	H	*i*-Pr	O	**21**	70	55:45
8	22	O	Ph	Ph	*i*-Pr	O	**23**	72	94:6

[a] Reactions were carried out in THF at −40 to −50 °C in the presence of 2.0−3.0 equiv of DMD [as a solution in acetone] and 10.0 equiv of the diene. For entries 1−3, 2.0 equiv of $ZnCl_2$ was used. All reactions were completed within 8 h. [b] All are isolated yields. [c] Endo ratios were determined by using ^1H and/or ^{13}C NMR.

endo selectivity. diastereoselectivity is modest → + $ZnCl_2$ or low temp or bulky chiral auxiliary

working model

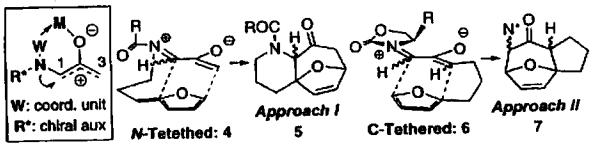


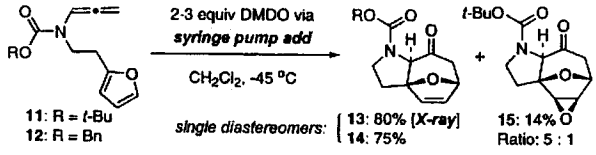
A vs B : to minimize dipole interaction

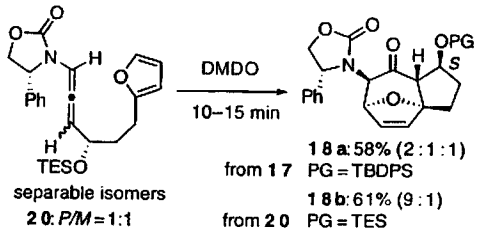
Zn^{2+} should enhance the conformational rigidity of the oxyallyl cation D

Figure 1.

intramolecular version







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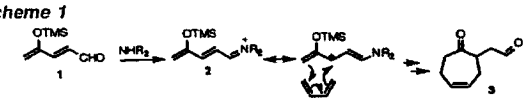
3. Catalytic Asymmetric [4+3] Cycloaddition — JACS 125, 2058(2003)
Harmata et al.

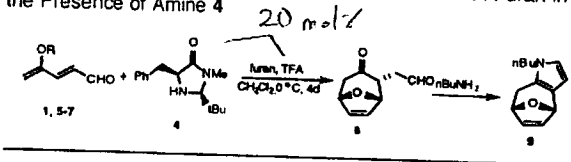
concept



catalyst activation by chiral iminium ion

results

Table 1. Reaction of 4-Trialkylsilyloxypentadienals with Furan in the Presence of Amine 4

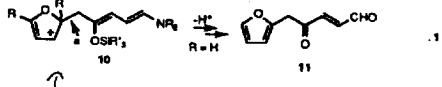


entry	educt, R	yield (%)[a]	ee[b]
1	1, TMS	8	50
2	5, TES	10	55
3	6, TBS	8	65
4	7, TIPS	0	

[a] Isolated yields for the endo diastereomer. [b] Enantiomeric excesses were determined by analysis of the *N*-butylpyrrole derivative of **12** using a Chiracel OD-H column.

endo only
low yield, modest ee's

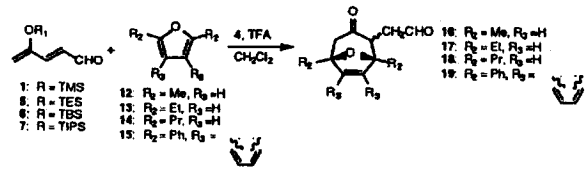
1 +  → desired product
↓
II + complex mixture



to suppress II → disubstituted furan

Stepwise procedure → II

Table 2. Asymmetric 4 + 3 Cycloaddition Reactions of Substituted Furans

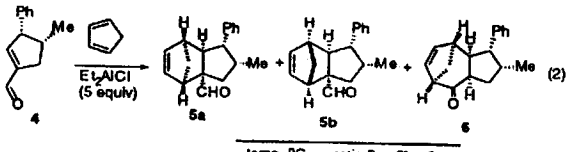


entry	R_1	R_2	R_3	time (h)	T °C	product	yield (%)	endo:exo	ee[a]
1	TMS	Me	H	36	−60	16	64	endo	87
2	TMS	Me	H	96	−78	16	64	endo	89
3	TES	Me	H	96	−60	16	51	endo	81
4	TBS	Me	H	96	−60	16	44	endo	80
5	TIPS	Me	H	96	−60	16	21	endo	90
6	TMS	Et	H	22	−60	17	55	endo	81
7	TBS	Et	H	91	−65	17	18	endo	87
8	TES	Et	H	91	−65	17	46	endo	84
9	TES	Pr	H	95	−65	18	74	endo	85
10	TMS	Pr	H	95	−65	18	33	endo	89
11	TMS	Ph		92	−35	19	56	3.7:1	endo 12% exo 68%

[a] Enantiomeric excesses were determined by analysis of the *N*-butylpyrrole derivative of the cycloadducts using a Chiracel OD-H or Chiralpak AD column.

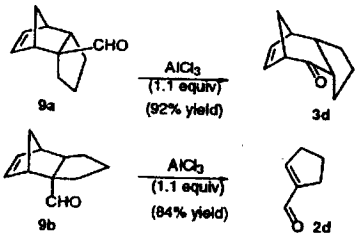
4. Tandem D-A / Ring Expansion — Davis et al JACS 126, 2692(2004)

(observations)



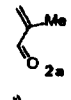
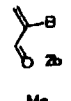
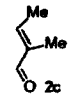
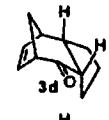
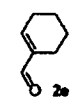
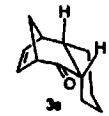
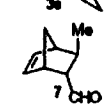
temp, °C	ratio 5a : 5b : 6
-78	84 : 16 : 0
-78 to 0	7 : 21 : 72

- diastereoselective
- Ring strain might be a factor as the reaction



Major exo isomer 9a underwent rearrangement, while minor endo isomer 9b underwent retro-D-A rxn. → (high selectivity
low yield (2c, 2e)

Table 1. [4 + 3] Cycloaddition of 1,3-Cyclopentadiene with α,β-Unsaturated Aldehydes[a]

substrate	product	yield, %[b]	de, %[c]
 2a	 3a	90	98
 2b	 3b	80	98
 2c	 3c	40	97
 2d	 3d	86	>98
 2e	 3e	21	>98
 2f	 7	71[d]	37

[a] Reaction conditions: 1.1 equiv of $AlCl_3$, 2.5 equiv of diene, −78 to 0 °C, CH_2Cl_2, 2 h. [b] Isolated yield after chromatographic purification. [c] The de was determined from a 500 MHz ^1H NMR spectrum of the crude reaction mixture. [d] Isolated yield of the mixture of *endo* and *exo* diastereomers.

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