Atropselective Synthesis of Axially Chiral Biaryl Compounds

literature Seminar (P2 1/2)

H. Kakei

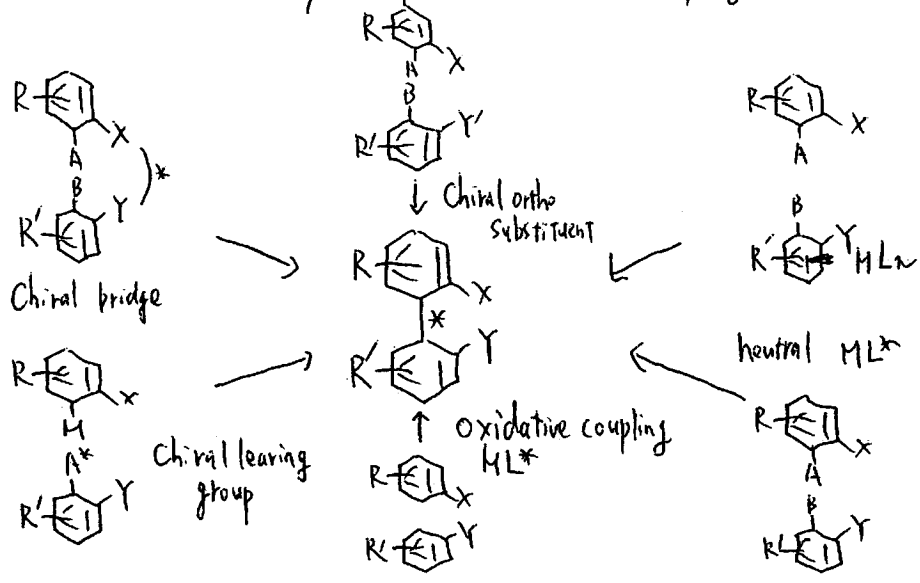
Axially chiral biaryl compounds are well recognized as a characteristic chemical class in organic synthesis due to their utility as efficient chiral ligands and key intermediates of biologically active compounds. Until now, various synthetic methods have been exploited to produce chiral biaryls.

In this seminar I will mainly talk about asymmetric biaryl synthesis by construction of an aromatic ring

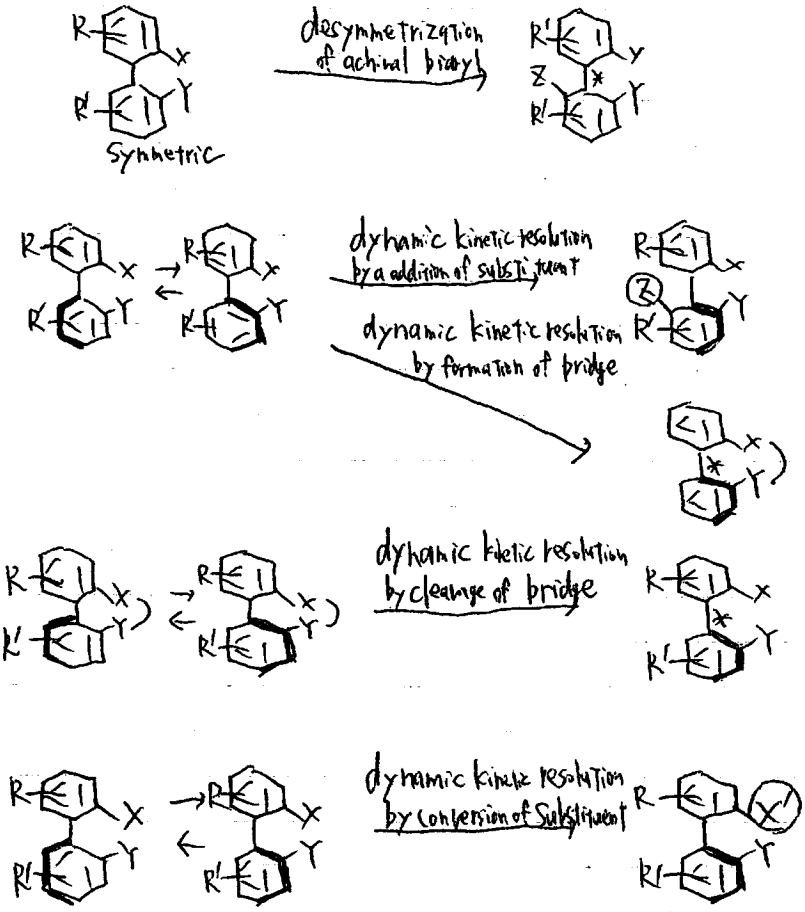
- Contents -

I. Introduction

(1) Biaryl Synthesis by Asymmetic C-C coupling



(2) Atroposelective transformations of prostereogenic biaryl compounds

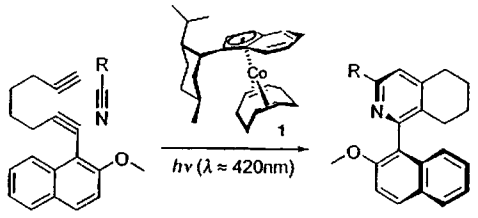


2. [2+2+2] Cyclo Addition

VIP **Asymmetric Catalysis**

A. Gutnov,* B. Heller,* C. Fischer, H.-J. Drexler, A. Spannenberg, B. Sundermann, C. Sundermann ——— 3795–3797

Cobalt(I)-Catalyzed Asymmetric [2+2+2] Cycloaddition of Alkynes and Nitriles: Synthesis of Enantiomerically Enriched Atropoisomers of 2-Arylpyridines



82–93 % *ee*

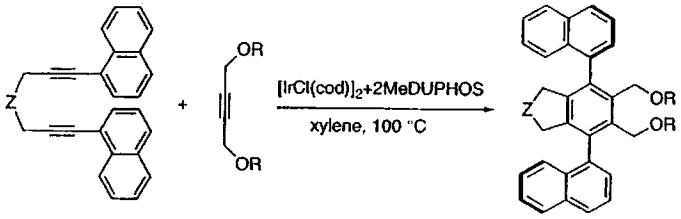
A new flavor of chiral induction in the [2+2+2] cycloaddition yielding pyridines: Atropoisomers were prepared in the reaction of alkynes and nitriles in the presence of 1 mol% chiral Co^I catalysts such as **1** with high yields and up to 93% *ee*.

8382 ■

Iridium Complex-Catalyzed Highly Enantio- and Diastereoselective [2+2+2] Cycloaddition for the Synthesis of Axially Chiral Teraryl Compounds

Takanori Shibata,* Takayoshi Fujimoto, Kazuhisa Yokota, and Kentaro Takagi

J. Am. Chem. Soc. **2004**, *126*, 8382–8383



Z= O, NTs, $C(CO_2Et)_2$, CH_2

up to >99.5% ee
dl/*meso* = >95/5

II Early Example

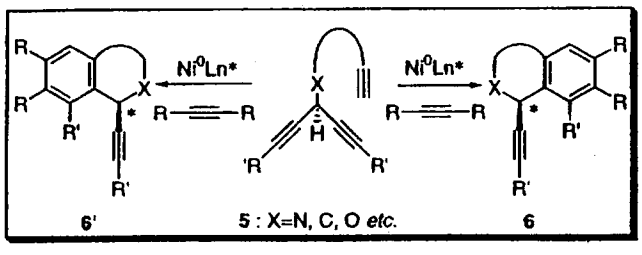
Asymmetric Synthesis of Isoindoline and Isoquinoline Derivatives Using Nickel(0)-Catalyzed [2 + 2 + 2] Cocyclization

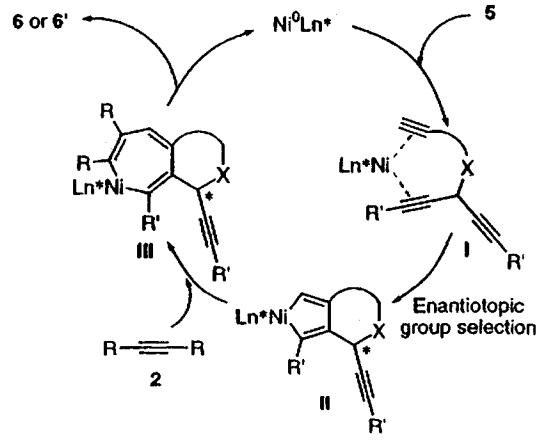
Yoshihiro Sato, Toyoki Nishimata, and Miwako Mori*

Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

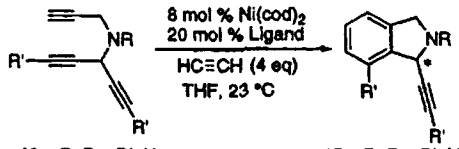
J. Org. Chem 1994, 59, 6132

Scheme 2





Scheme 5

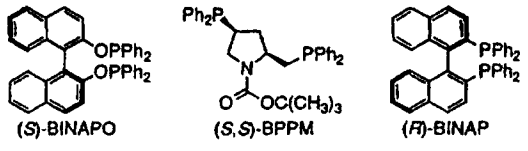


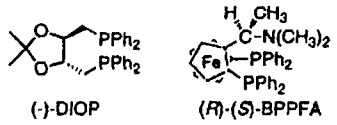
12a: R=Bn, R'=H
13a: R=Tr, R'=TMS
14a: R=Tr, R'=H

15a: R=Bn, R'=H
16a: R=Tr, R'=TMS
17a: R=Tr, R'=H
18a: R=Bz, R'=TMS

Table 1. Catalytic Asymmetric [2 + 2 + 2] Cocyclization of 13a and 14a

run	substrate	ligand	time (hr)	yield (%)	ee (%)	SM recover (%)
1	**14a**	dppb	1.5	74	—	—
2		(*S*)-BINAPO	16	68	12	—
3		(*S,S*)-BPPM	2	82	45	—
4	**13a**	dppb	5	83	—	—
5		(*R*)-BINAP	140	57	22	18
6		(*S*)-BINAPO	115	52	18	14
7		(-)-DIOP	18	87	0	—
8		(*S,S*)-BPPM	18	92	60	—
9		(*R*)-(*S*)-BPPFA	150	52	73	33





[2] Previous Studies about Co-Catalyzed Synthesis of Pyridines

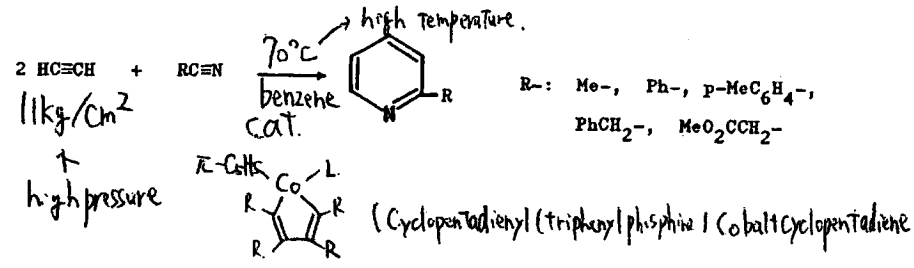
(1) First example

COBALT-CATALYZED SYNTHESIS OF PYRIDINES FROM ACETYLENES AND NITRILES

Tetrahedron Lett. 1973. 36. 3383

Yasuo Wakatsuki and Hiroshi Yamazaki

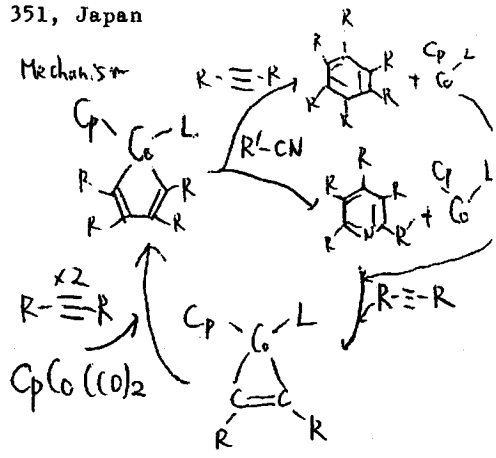
The Institute of Physical and Chemical Research, Wako-shi, Saitama 351, Japan



11kg/cm² ↑ high pressure

(Cyclopentadienyl(triphenylphosphine)Cobaltcyclopentadiene

R=Me y. 24%



(2) Improvement

PHOTOASSISTED COCYCLIZATION OF ACETYLENE AND NITRILES CATALYZED BY COBALT COMPLEXES AT AMBIENT TEMPERATURE AND NORMAL PRESSURE

Tetrahedron Lett. 1989 30. 1229

W. Schulz*, H. Pracejus, and G. Oehme

Central Institute of Organic Chemistry, Division of Complex Catalysis, Academy of Science of GDR, Buchbinderstr. 5-6, Rostock, GDR-2500

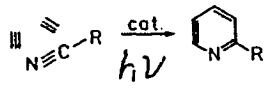


Table 1 Catalytic cocyclization of acetylene and nitriles

Entry	catalyst[a] (mole%)	nitrile[b] (%conversion)	reaction time in h	reaction temper.	pyridine (% selectivity)[c]	turnover number[d]	remarks[e]
1	A ($2.95\cdot10^{-4}$)	AN (0.47)	3	40 °C	2-Me- (98.1)	1590	in the dark
2	A ($1.3\cdot10^{-4}$)	AN (0.88)	3	40 °C	2-Me- (97.7)	6550	diffuse daylight
3	A ($1.1\cdot10^{-4}$)	AN (1.17)	3	40 °C	2-Me- (97.9)	10490	sunlight
4	A ($1.1\cdot10^{-4}$)	AN (2.41)	1	25 °C	2-Me- (98.8)	16640	Hg-lamp (125 W)
5	B ($4.1\cdot10^{-4}$)	AN (1.57)	2	40 °C	2-Me- (98.3)	3860	254-580 nm
6	B ($3.8\cdot10^{-4}$)	AN (2.22)	2	40 °C	2-Me- (99.0)	5930	320-370 nm
7	B ($3.6\cdot10^{-4}$)	AN (4.35)	2	40 °C	2-Me- (99.3)	11584	> 400 nm
8	B ($1.8\cdot10^{-3}$)	PN (12.73)	2	50 °C	2-Et- (99.6)	7240	
9	B ($1.8\cdot10^{-3}$)	PN (12.9)	2	25 °C	2-Et- (99.6)	7370	Hg-lamp (125 W),
10	B ($1.8\cdot10^{-3}$)	PN (12.5)	2	-60 °C	2-Et- (94.5)	7170	internal,
11	C ($2.1\cdot10^{-3}$)	PN (19.3)	2	15 °C	2-Et- (99.7)	9340	filtered by
12	D ($1.9\cdot10^{-3}$)	PN (13.73)	2	15 °C	2-Et- (99.6)	7430	Rasotherm
13	E ($1.7\cdot10^{-3}$)	PN (12.46)	2	15 °C	2-Et- (99.6)	7220	glass
14	F ($1.7\cdot10^{-3}$)	PN (10.7)	2	15 °C	2-Et- (99.6)	6510	
15	B ($1.5\cdot10^{-3}$)	PN (20.25)	0.5	15 °C	2-Et- (98.8)	13400	Hg-lamps, external
16	B ($1.3\cdot10^{-4}$)	PN (8.85)	0.5	15 °C	2-Et- (98.5)	66200	500 W, internal 125 W
17	B ($8.4\cdot10^{-3}$)	PN (28.3)	5 min	15 °C	2-Et- (99.6)	3350	halogen lamps,
18	B ($8.4\cdot10^{-3}$)	PN (43.34)	0.5	15 °C	2-Et- (99.1)	5100	external 800 W

a) A = $(C_5H_5)Co(C_2H_4)_2$, B = $(C_5H_5)Co(cod)$, C = $(Ph_4C_5H)Co(cod)$, D = $(CH_3OCOC_5H_4)Co(cod)$
E = $(CH_3COC_5H_4)Co(cod)$, F = $(PhCOC_5H_4)Co(cod)$

b) AN = acetonitrile, PN = propionitrile

c) selectivity in relation to benzene

d) number of catalytic cycles until catalyst deactivation

e) entries 1-16: 1.5 to 5.3 moles nitrile; entries 17-18: 0.028 mole nitrile as substrate

Entry 1-4
Comparison of the influence of light
Entry 5-7
The effects of wave length

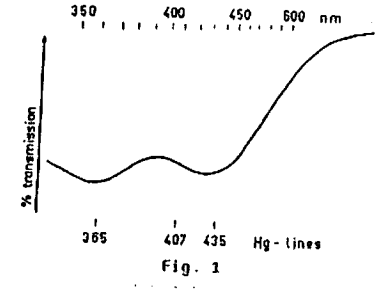


Fig. 1

Entry 8-10
Temp. Effects
Entry 11-14
Effects of Cp-Ligand under Hg-lamp
Entry 15-18
Strength effects of UV-lamp

(3) Mechanism investigations (The effects of light enhancement)

Systematic investigations of the photocatalytic alkyne–nitrile heterotrimerisation to pyridine

J. Mol Cat. A: Chem. 110.1996.211

B. Heller [a,*], D. Heller [b], G. Oehme [a]

[a] Institut für Organische Katalyseforschung an der Universität Rostock e.V., Buchbinderstraße 5/6, D-18055 Rostock, Germany
[b] Max-Planck-Gesellschaft, AG "Asymmetrische Katalyse" an der Universität Rostock, Buchbinderstraße 5/6, D-18055 Rostock, Germany

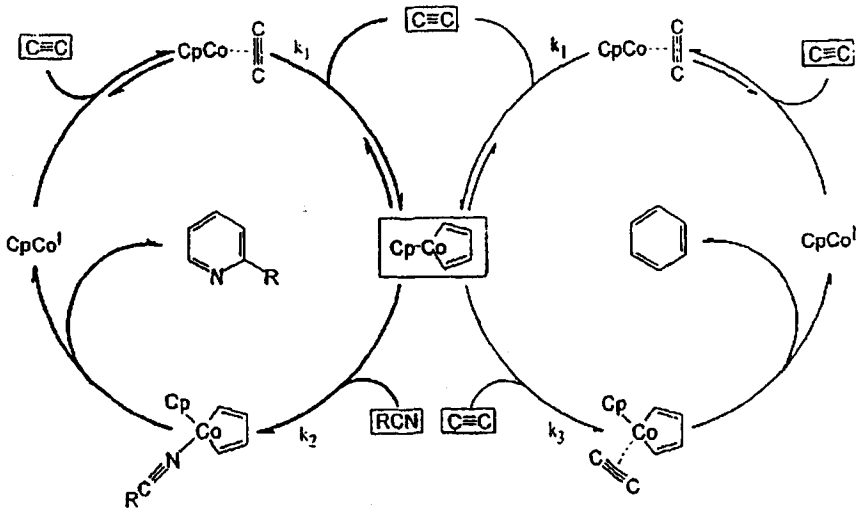


Fig. 1. Reaction scheme for the thermally induced pyridine synthesis according to Bönnemann et al. [13,14].

$$\frac{d[Nit]}{d[Ben]} = \frac{-d[P]}{d[Ben]} = \frac{-k_2[Nit][Cp\text{-}Co]}{k_3[C\equiv C][Cp\text{-}Co]} = \frac{-k_2[Nit]}{k_3[C\equiv C]} \quad (1)$$

If throughout the reaction $[C\equiv C]$ is kept constant and the initial concentration of $[Ben]_0 = 0$

$$d[Ben] = \frac{-k_3[C\equiv C]}{k_2[Nit]}\, d[Nit] \rightarrow \int_0^t d[Ben]\,dt = [Ben] = \frac{-k_3[C\equiv C]}{k_2}\int_0^t \frac{d[Nit]}{[Nit]}\,dt$$

$$= \frac{-k_3[C\equiv C]}{k_2}\left[\ln[Nit]\right]_0^t$$

$$= \frac{-k_3[C\equiv C]}{k_2}\left\{\ln[Nit] - \ln[Nit]_0\right\}$$

$$[Ben] = \underbrace{\frac{-k_3[C\equiv C]}{k_2}}_{\text{const.}} \ln\left(\frac{[Nit]}{[Nit]_0}\right) \quad (2)$$

(2) accorded with experimental results

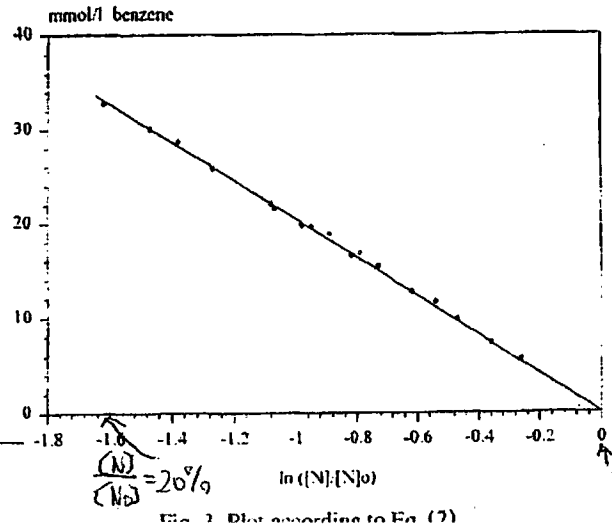


Fig. 2. Plot according to Eq. (2)

$[Nit]_0 = [Nit] + [Py]$ ... (3)

$[T_{C\equiv C}]$ ... Total C≡C consumption

$[T_{C\equiv C}] = 3 \cdot [Ben] + 2[Py]$ ... (4)

(2) transform $[Ben] = Const \times \ln\left(\frac{[Nit]}{[Nit]_0}\right)$

$[Py] = \frac{1}{2}\left([T_{C\equiv C}] + 3 \cdot const \cdot \ln\left(\frac{[Nit]_0 - [Py]}{[Nit]_0}\right)\right)$ ... (5)

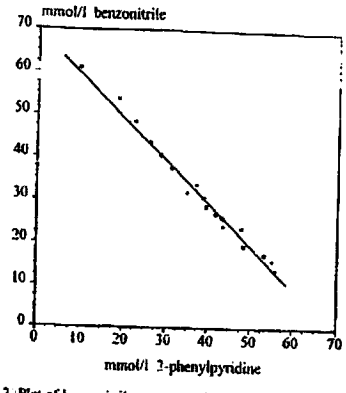


Fig. 2. Plot of benzonitrile- versus 3-phenylpyridine-concentration according to Eq. (3).

→ This results accorded with (3)

From $[T_{C\equiv C}]$ and $[Nit]_0$

The values of $[Py]$, $[Ben]$ $[Nit]$

were decided ↘

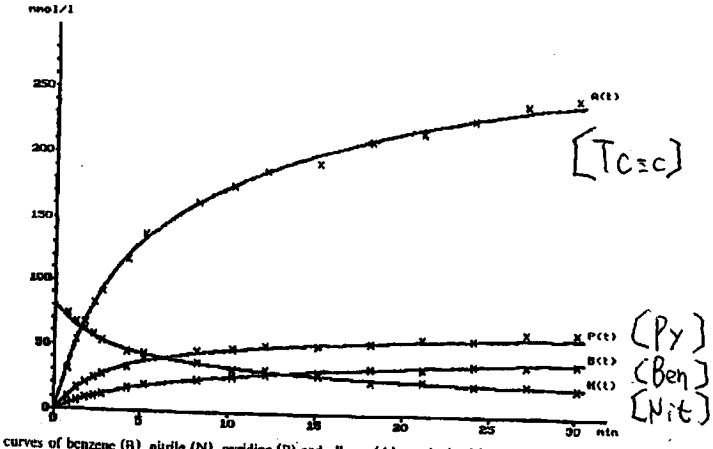


Fig. 4. Graphical curves of benzene (B), nitrile (N), pyridine (P) and alkyne (A), as obtained by GC analysis (– × –) (ethyne according stoichiometry), and from the measured ethyne absorption (filled line) (experimental conditions: 1.21 mmol nitrile, 15 ml of solution).

In the dark reaction the formation of metallacyclic intermediate was the rate-determining step., the nitrile reaction order was "0"

The linear relationship between the rates of nitrile consumption and initial nitrile concentrations show the formation of the metallacyclic intermediate is not

but the rate-limiting step is the reaction of this intermediate with the nitrile, giving thus rise to the observed first-order kinetics.

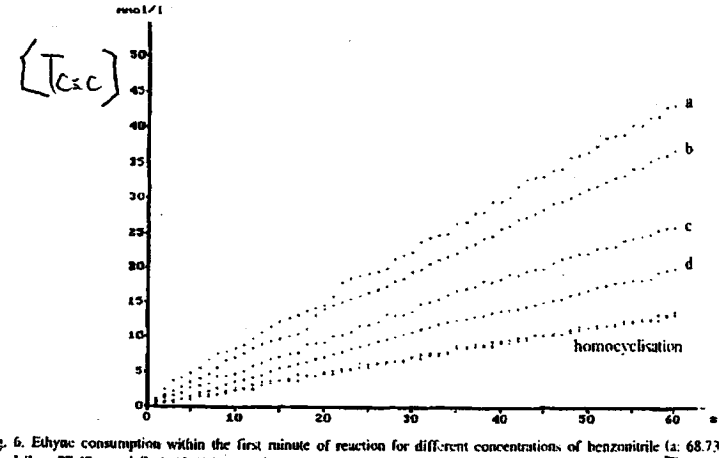


Fig. 6. Ethyne consumption within the first minute of reaction for different concentrations of benzonitrile (a: 68.73 mmol/l; b: 55.00 mmol/l; c: 27.47 mmol/l; d: 13.73 mmol/l).

→ irradiation accelerate the formation of the Cobaltacyclopentadi

[3] Asymmetic [2+2+2] Cycloaddition catalyzed by Co(I) catalyst

Asymmetric Catalysis

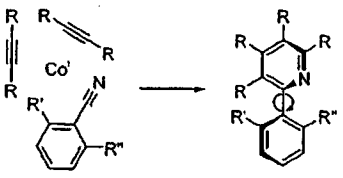
Cobalt(I)-Catalyzed Asymmetric [2+2+2] Cycloaddition of Alkynes and Nitriles: Synthesis of Enantiomerically Enriched Atropoisomers of 2-Arylpyridines**

Andrey Gutnov, Barbara Heller,* Christine Fischer, Hans-Joachim Drexler, Anke Spannenberg, Bernd Sundermann, and Corinna Sundermann*

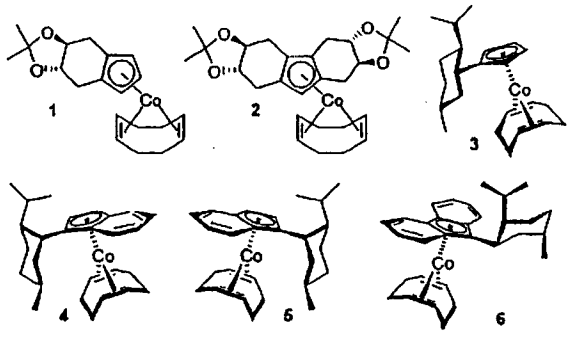
In memory of Oleg Okhlobystin

Angew. Chem. Int Ed. 2004. 43. 3795

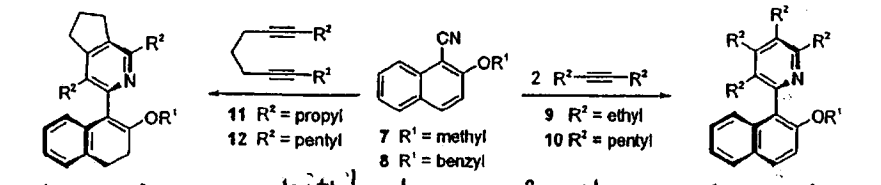
Strategy



Scheme 1. [2+2+2] Cycloaddition giving axially chiral 2-arylpyridines.



Scheme 2. Chiral cobalt(I) complexes employed.



16 R^1 = methyl; R^2 = pentyl
17 R^1 = methyl; R^2 = propyl
18 R^1 = benzyl; R^2 = pentyl

11 R^2 = propyl
12 R^2 = pentyl

7 R^1 = methyl
8 R^1 = benzyl

9 R^2 = ethyl
10 R^2 = pentyl

13 R^1 = methyl; R^2 = ethyl
14 R^1 = benzyl; R^2 = ethyl
15 R^1 = methyl; R^2 = pentyl

nitrile 1
alkyne 2.2
catalyst 0.1
20°C, 9hr
visible light

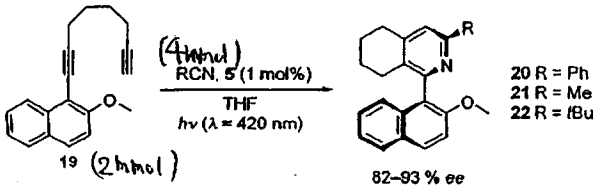
Scheme 3. Asymmetric cocycloaddition of internal alkynes and 1-naphthonitriles.

- The enantioselectivity of the reaction doesn't depend on the solvent
- The duration of irradiation and the amount of catalyst have no influence
- Decreasing temperature gave poor yield

Table 1: [2+2+2] Cycloaddition of 2-alkoxy-1-naphthonitriles and stituted alkynes.

Run[a]	Cat.	Prod.	Yield [%][b]	Sel. [%
1	1	13	14	45 (+)
2	2	13	traces	–
3	3[d]	13	34	19 (+)
4	4	13	11	63 (+)
5	5	13	10	64 (–)
6[c]	5	13	2	71 (–)
7	6	13	traces	–
8	1	16	81	32 (+)
9	1	15	11	40 (–)
10	4	14	3	59 (+)
11	4	18	7	39 (+)
12	4	16	32	37 (+)
13	4	17	8	31 (+)
14	5	16	33	38 (–)
15	5	17	8	32 (–)
16	5	15	2	63 (+)

[a] The reaction was carried out in THF at 20 °C for 9 h and irradiated w visible light; molar ratio: [nitrile]/[alkyne]/[catalyst] = 1:2.2:0.1 unl indicated otherwise; analytical data and synthetic procedures for the n compounds are given in Supporting Information. [b] Yields of isolat products. [c] Determined by HPLC on a chiral stationary phase (see t Supporting Information for details); direction of optical rotation given parentheses: $c = 0.1$, toluene, 25 °C. [d] 5 mol% catalyst. [f] Reacti temperature 3 °C.

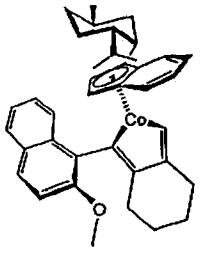


19 (2 mmol)

20 R = Ph
21 R = Me
22 R = tBu

82–93 % *ee*

Scheme 4. Asymmetric cycloaddition giving optically enriched 1-aryl-5,6,7,8-tetrahydroisoquinolines.



Scheme 5. The intermediate cobaltacyclopentadiene.

Table 2: Enantioselectivities and yields in the syntheses of isoquinolines 20–22.

Run	Prod.	T [°C]	Yield [%]	Sel. [% *ee*]
1	20	20	79[a] (49[b])	82[c] (> 98[b])
2	20	3	86[a] (57[b])	89[c] (> 98[b])
3	20	–20	86[a] (56[b])	93[c] (> 98[b])
4	21	3	88[a] (54[b])	88[c] (> 98[b])
5	22	3	74[a] (46[b])	88[c] (> 98[b])

[a] Yield after chromatography. [b] Determined after recrystallization. [c] Measured in reaction mixture.

4 Previous Studies about Iridium-catalyzed reaction

(1) Iridium catalyzed enantioselective Pauson-Khand-Type reaction

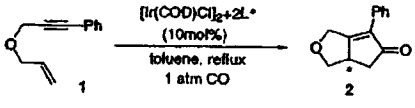
Iridium–Chiral Diphosphine Complex Catalyzed Highly Enantioselective Pauson-Khand-Type Reaction

Takanori Shibata* and Kentaro Takagi

Department of Chemistry, Faculty of Science Okayama University, Okayama 700-8530, Japan

J. Am. Chem Soc 2000. 122. 9852

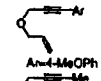
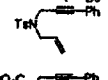
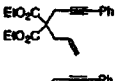
Table 1. Catalytic Enantioselective Carbonylative Coupling of **1**



entry	L*	time/h	yield/%	ee/%[a]
1	(*S*)-BINAP	12	64	86(*S*)
2	(*R*)-BINAP	12	62	88(*R*)
3	(*S*)-tolBINAP	18	83	93(*S*)
4[b]	(*S*)-tolBINAP	24	75	91(*S*)

[a] Ee was determined by HPLC using the Daicel chiral column (Chiralpak AD). Absolute configuration was determined by the comparison of specific rotation of obtained **2** with that in the literature.[9b] [b] 5 mol % of $[Ir(COD)Cl]_2$ was used.

Table 2. Catalytic Enantioselective Carbonylative Coupling of Various Enynes[a]

entry	enyne	cyclopentenone	time/h	yield/%	ee/%[b]
1			20	80	96
2			20	61	98
3			48	75	97
4			20	54	90
5			24	85	95
6			36	51	88
7			72	74	84
8			24	30	88
9[c]			24	51	82

[a] Chiral catalyst: $[Ir(COD)Cl]_2$ + 2(*S*)-tolBINAP (10 mol %). The reaction was performed under atmospheric pressure of carbon monoxide in refluxed toluene, if otherwise noted. [b] Ee was determined by HPLC using Daicel chiral columns (Chiralpak AS for entries 1–3, 6 and 7, Chiralcel OD for entries 4 and 5, Chiralpak AD for enries 8 and 9. [c] The reaction was perfomed in refluxed xylene.

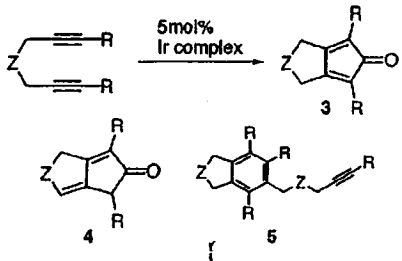
(2) Iridium catalyzed carbonylative Alkyne-Alkyne couply

Iridium Complex Catalyzed Carbonylative Alkyne–Alkyne Coupling for the Synthesis of Cyclopentadienones

Org. Lett. 2001 1217

Takanori Shibata,* Koji Yamashita, Hiroyuki Ishida, and Kentaro Takagi

Table 2. Iridium Complex-Catalyzed Carbonylative Coupling of Various Diynes



entry[a]	R	Z	catalyst[b]	yield (%)
1	Ph	$C(CO_2Bn)_2$	A	86 (3a)
2	Ph	$C(CO_2Bn)_2$	B	70[c] (3a)
3[d]	Ph	$C(CO_2Bn)_2$	A	85 (3a)
4	Ph	$C(CO_2Et)_2$	A	99 (3b)
5	Ph	$C(CO_2t\text{-}Bu)_2$	A	92 (3c)
6	4-MeO-Ph	$C(CO_2Bn)_2$	A	94 (3d)
7	4-Cl-Ph	$C(CO_2Bn)_2$	A	79[e] (3e)
8	4-MeO_2C-Ph	$C(CO_2Bn)_2$	A	89[f] (4f)
9	Ph	CH_2	A	79 (3g)
10	Ph	O	A	65 (3h)

[a] Reaction conditions: CO 1 atm, xylene 120 °C, 2–7 h, unless otherwise noted. [b] A, $IrCl(CO)(PPh_3)_2$; B, IrCl(COD)(dppp). [c] **4a** (5%) and **5a** (6%) are also obtained. [d] The reaction was examined under a mixture of CO (0.2 atm) and Ar (0.8 atm). [e] **4e** (20%) is also obtained. [f] A mixture of **3f** and **4f** (1:2) was obtained. **3f** was isomerized into **4f**, which was isolated and characterized.

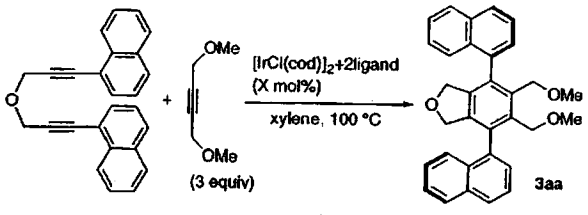
↳ [2+2+2] Cycloaddition occured

[5] Asymmetric [2+2+2] cycloaddition catalyzed by Ir(I) catalyst

Iridium Complex-Catalyzed Highly Enantio- and Diastereoselective [2+2+2] Cycloaddition for the Synthesis of Axially Chiral Teraryl Compounds

Takanori Shibata,*,† Takayoshi Fujimoto,‡ Kazuhisa Yokota,‡ and Kentaro Takagi‡

Table 1. Asymmetric [2+2+2] Cycloaddition Using Chiral Iridium Complexes

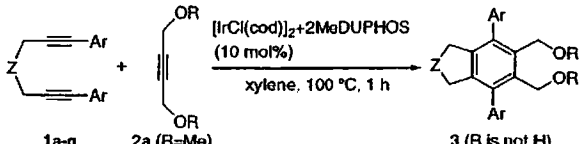


1a 2a + 3aa-*meso*

entry	ligand	X/mol%	time/h	yield/%	*dl*/*meso*	ee/%
1	(*S*)-BINAP	10	4	31	60/40	6
2	(*S,S*)-BDPP	10	6	39	45/55	51
3	(*S,S*)-MeDUPHOS	10	1	83	>95/5	99.6
4	(*S,S*)-EtDUPHOS	10	1	75	>95/5	99.8
5	(*R,R*)-MeDUPHOS	10	1	88	>95/5	99.6[a]
6	(*S,S*)-MeDUPHOS	5	1	83	>95/5	99.0
7	(*S,S*)-MeDUPHOS	2	1	89	>95/5	99.3
8	(*S,S*)-MeDUPHOS	0.5	3	84	98/2	99.1

[a] An opposite enantiomer to the above structure of **3aa** was obtained.

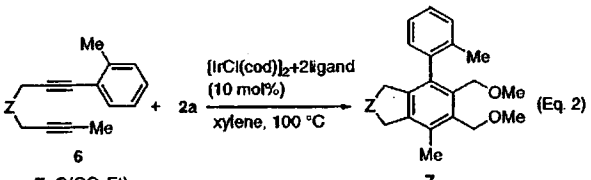
Table 2. Asymmetric [2+2+2] Cycloaddition of Various α,ω-Diynes and Monoalkynes



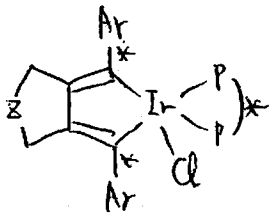
1a-g 2a (R=Me) 2b (R=THP) 2c (R=TBS) 2d (R=MOM) 3 (R is not H) 4 (R= H)

entry	Ar	Z	diyne	R	yield/%[a]	ee/%
1	1-naphthyl	O	1a	THP	76 (4a)[b]	99.5[b]
2	1-naphthyl	O	1a	TBS	74 (3ac)	99.5[c]
3	1-naphthyl	O	1a	MOM	76 (3ad)[d]	98.5
4	2-MeC_6H_4	O	1b	Me	85 (3ba)	99.6
5	2-Cl C_6H_4	O	1c	Me	85 (3ca)	97.7
6	4-MeO-1-naphthyl	O	1d	Me	72 (3da)	99.4
7	1-naphthyl	NTs	1e	Me	92 (3ea)	99.4
8	1-naphthyl	NTs	1e	THP	97 (4e)[b]	99.1[b]
9	1-naphthyl	$C(CO_2Et)_2$	1f	Me	77 (3fa)	>99.8
10	1-naphthyl	CH_2	1g	Me	96 (3ga)	>99.8
11	1-naphthyl	CH_2	1g	TBS	77 (3gc)[e]	98.6[e]

[a] Only *dl* isomer was detected by NMR spectrum, except entries 3 and 11. [b] Yield and ee were determined as diol **4a** or **4e** after deprotection using PPTS in EtOH. [c] Ee was determined as diol **4a** or **4g** after deprotection using TBAF in THF. [d] *dl*/*meso*= 93/7. [e] *dl*/*meso* = 91/9.



(Eq. 2) → biaryl product was obtained in moderate ee



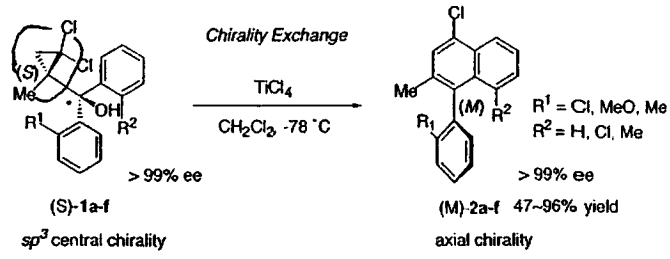
→ metallacyclopentadiene intermediate

3. Chirality Exchange

Chirality Exchange from sp³ Central Chirality to Axial Chirality: Benzannulation of Optically Active Diaryl-2,2-dichlorocyclopropylmethanols to Axially Chiral α-Arylnaphthalenes

Yoshinori Nishii,* Kazunori Wakasugi, Keisuke Koga, and Yoo Tanabe*

J. Am. Chem. Soc. **2004**, *126*, 5358−5359



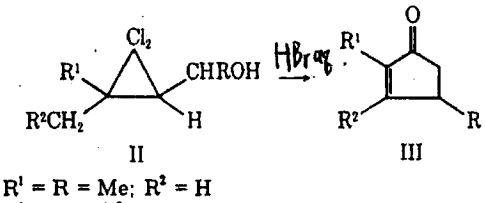
II Representative reactions using gem-Dihalocyclopropanes

(1) Thermal reactions

Acid-Catalyzed Reaction of Dichlorocyclopropylcarbinols. Preparation of 2-Cyclopentenones

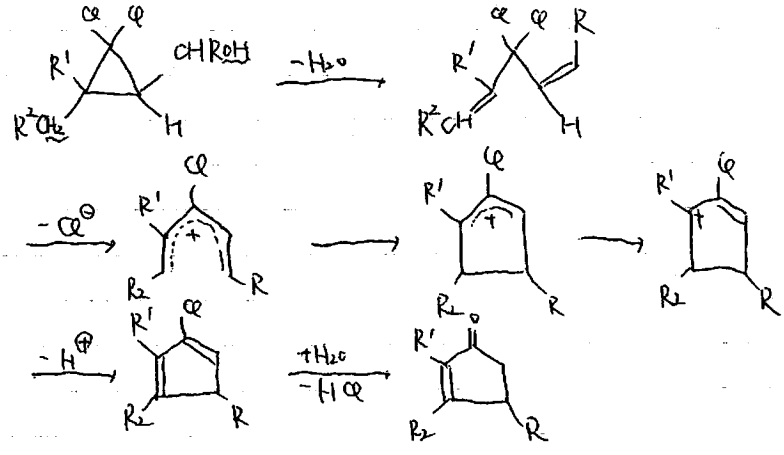
Tamejiro Hiyama,* Masao Tsukanaka, Hitosi Nozaki
Department of Industrial Chemistry, Kyoto University
Yoshida, Kyoto, 606 Japan
Received March 2, 1974

J. Am. Chem. Soc. 1974, 96, 3713



a, $R^1 = R = Me$; $R^2 = H$
b, $R^1 = Me$; $R^2 = R = H$
c, $R^1 = Me$; $R^2 = n\text{-}C_4H_9$; $R = H$
d, $R^1 = Me$; $R^2 = n\text{-}C_5H_{11}$; $R = H$
e, $R^1 = Me$; $R^2 = CH_2{=}CHCH_2$; $R = H$
f, $R^1,R^2 = -(CH_2)_{10}-$; $R = H$

Mechanism



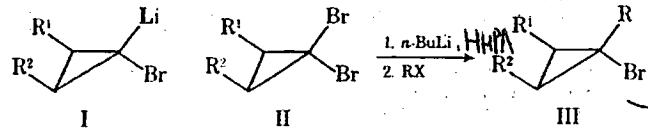
(2) Halogen-Metal Exchange and Further Reactions of 1-Halo-1-metallocyclopropanes

Generation of a Carbenoid

Stereoselective Alkylation of 1-Lithiocyclopropyl Bromides

Katuzi Kitatani, Tamejiro Hiyama,* Hitosi Nozaki
Department of Industrial Chemistry, Kyoto University
Yoshida, Kyoto 606, Japan
Received November 16, 1974

J. Am. Chem. Soc 1975, 97, 949



Thermodynamically prefered configuration

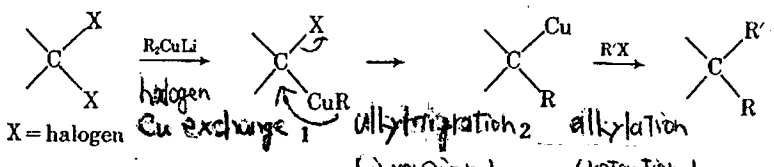
Generation of Ate complex.

Ⓐ Cu (Dialkylation)

Stereoselective One-Pot Dialkylation of *gem*-Dihalocyclopropanes. A Simple Route to *dl*-Sesquicarene and *dl*-Sirenin

Katuzi Kitatani, Tamejiro Hiyama,* Hitosi Nozaki
Department of Industrial Chemistry, Kyoto University
Yoshida, Kyoto 606, Japan
Received December 15, 1975

J. Am. Chem. Soc. 1976. 98. 2362



Stereoselectively proceeded.

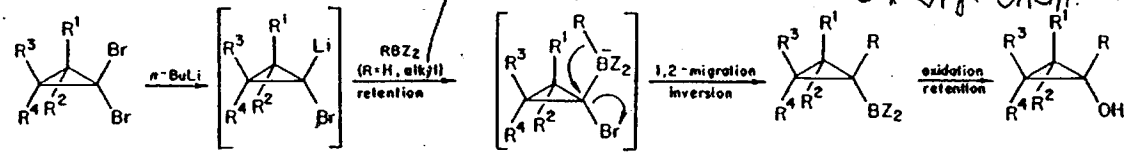
Ⓑ B (cyclopropanol synthesis)

Applications of Cyclopropylboranes in Organic Synthesis. 1. A Stereocontrolled Route to Substituted Cyclopropanol Derivatives

Rick L. Danheiser,*[11] Ann C. Savoca
Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139
Received March 28, 1985

J. Org. Chem. 1985. 50. 2401

Scheme I Me. Et. cHex

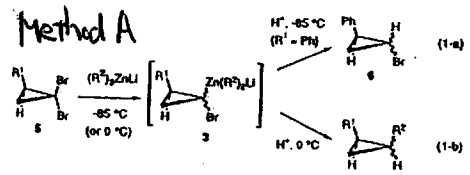


Ⓒ Zn (Stereoselective dialkylation)

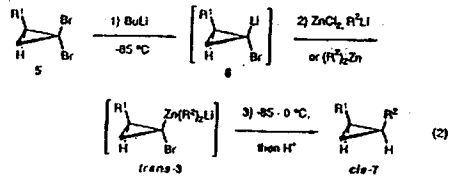
Stereoselective Carbon–Carbon Bond-Forming Reaction of 1,1-Dibromocyclopropanes via 1-Halocyclopropylzincates

Toshiro Harada,* Takeshi Katsuhira, Kazuhiro Hattori, and Akira Oku*
Department of Chemistry, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto 606, Japan
J. Org. Chem. 1993. 58. 2958

Method A

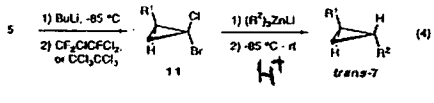


Method B (mixture)



(cis-selective)

Method C



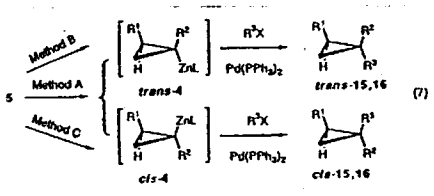
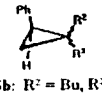
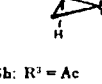


Table III. Stereoselective Synthesis of 1-Alkylcyclopropyl Ketones 15

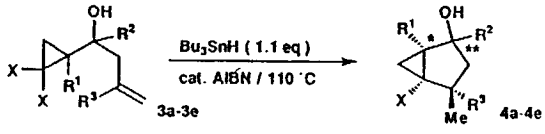
entry	substrate	R^2	electrophile	method	product	yield[a] (%)	trans:cis
1	5a	Bu	AcCl	A	15: R^2 = Bu, R^3 = Ac	76	1:1.9
2				B-1		74	16:1
3				C		50	1:7.0
4	5a	Bu	PhCOCl	A	15b: R^2 = Bu, R^3 = PhCO	58	2.1:1
5				B-1		50	38:1
6	5a	Bu	EtOCOCl	A	15c: R^2 = Bu, R^3 = EtOCO	59	2.5:1
7				B-1		58	60:1
8				C		45	1:28
9	5a	Et	AcCl	B-2	15d: R^2 = Et, R^3 = Ac	80	7.7:1
10	5a	^{i}Bu	AcCl	B-1	15e: R^2 = ^{i}Bu, R^3 = Ac	74	c
11	5a	^{t}Bu	AcCl	B-1	15f: R^2 = ^{t}Bu, R^3 = Ac	50	6.7:1
12	5b	Bu	AcCl	A	15g: 	96	2.4:1
13				B-1		65	5.7:1
14				C		52	1:21
15	5c	Bu	AcCl	A	15h: R^3 = Ac	70	1.4:1
16				B-1		75	11:1
17				C		66	1:32
18	5c	Bu	PhCOCl	A	15i: R^3 = PhCO	66	1.4:1
19	5e	Bu	AcCl	A	15j: 	64	

(3) Radical Cyclization

A Novel and Regioselective Radical Cyclization of *gem*-Dihalocyclopropyl Substituted Alkenes and Alkynes Using Tributyltin Hydride and Catalytic AIBN

Yoo TANABE,* Yoshinori NISHII, and Ken-ichi WAKIMURA
School of Science, Kwansei Gakuin University, 1-1-155 Uegahara, Nishinomiya, Hyogo 662

Chem Lett. 1994. 1757



→ 5-exo selective.
Anti selective (X ↔ Me)

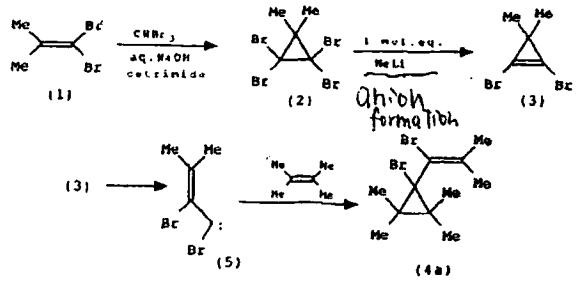
(4) Dehalogenation (Formation of cyclopropene)

The Generation and Trapping of 1,2-Dibromo-3-methylbut-2-en-1-ylidenes

by Ahmad R. Al Dulayymi, Juma'a R. Al Dulayymi, Mark S. Baird* and Leela Rajaram

Department of Chemistry, University of Wales, Bangor, Gwynedd, LL57 2UW

Tetrahedron 1995. 51. 8371



Vinyl carbenes(5) were generated from cyclopropene (3).

[2] Reactions of gem-Dihalocyclopropanes mediated by Lewis Acids

(1) Early Studies

EINE EINFACHE INDENSYNTHESE AUS DIHALOGENCYCLOPROPANEN

J. Buddrus und F. Nerdel

Technische Universität Berlin | Lehrstuhl für Theoretische Organische Chemie

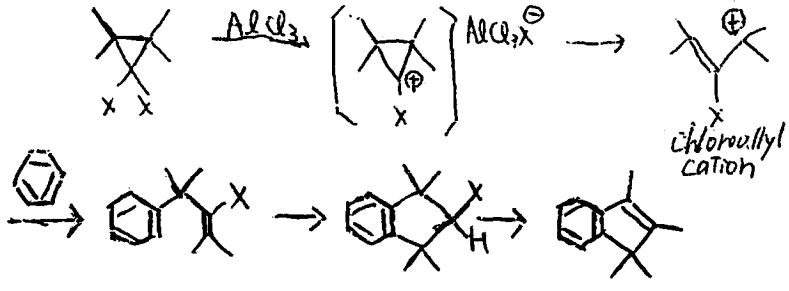
TL. 1965. 3197

Chemistry of *gem*-Dihalocyclopropanes. III.[1] A New Synthesis of Indenes

LARS SKATTEBØL AND BERNICE BOULETTE

Union Carbide Research Institute, Tarrytown, New York

J. O. C. 1966. 31. 81.



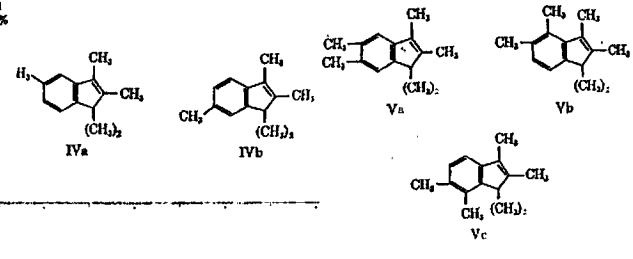
In the presence of Lewis acid, gem-dichlorocyclopropanes undergo ring opening to produce the chloro allyl cation, which can react with aromatic ring in a Friedel-Crafts-type reaction.

TABLE I

INDENES FROM *gem*-DIBROMOCYCLOPROPANES AND AROMATIC COMPOUNDS

gem-Dibromocyclopropane derivative	Aromatic compd.	Products (%)	Total yield, %
1,1-Dibromotetramethylcyclopropane (I)	Benzene	1,1,2,3-Tetramethylindene (II)	80
1,1-Dibromotetramethylcyclopropane (I)	Toluene	1,1,2,3,5-Pentamethylindene (IVa) (70)[a]	81
1,1-Dibromotetramethylcyclopropane (I)		1,1,2,3,6-Pentamethylindene (IVb) (30)[a]	
1,1-Dibromotetramethylcyclopropane (I)	*o*-Xylene	1,1,2,3,5,6-Hexamethylindene (Va) (60)	79
		1,1,2,3,4,5-Hexamethylindene (Vb)	
		1,1,2,3,6,7-Hexamethylindene (Vc) (40)[b]	
1,1-Dibromo-2,2-dimethylcyclopropane (VI)	Benzene	2,3-Dimethylindene (VII)	56
1,1-Dibromotrimethylcyclopropane (VIII)	Benzene	1,2,3-Trimethylindene (IX)	54
1,1-Dibromo-2-phenylcyclopropane (X)	Benzene	3-Phenylindene (XI)	25

[a] Approximate values. [b] Compounds Vb and Vc combined.

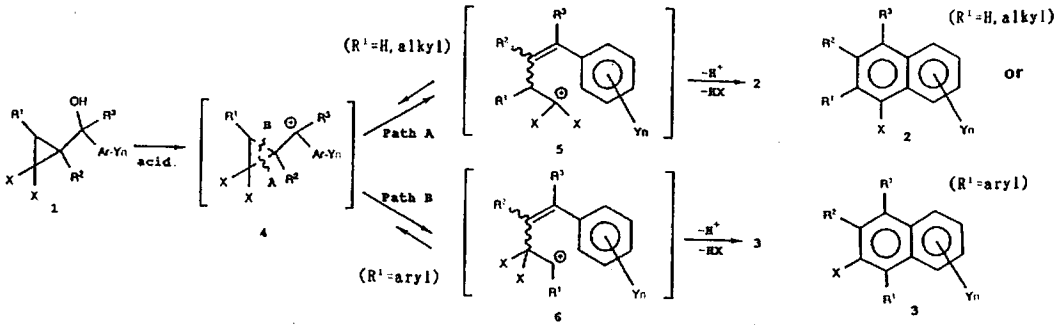


(2) Regioselective synthesis of α- or β- halonaphthalenes (1-) (2-) using Aryl dihalocyclopropyl methanols

Tetrahedron Lett 1990. 31. 6883.

A NOVEL SYNTHESIS OF α- AND β-HALONAPHTHALENES *VIA* REGIOSELECTIVE RING CLEAVAGE OF ARYL(*gem*-DIHALOCYCLOPROPYL)METHANOLS AND ITS APPLICATION TO TOTAL SYNTHESIS OF LIGNAN LACTONES, *JUSTICIDIN E* AND *TAIWANIN C*

Shinzo Seko, Yoo Tanabe,* and Gohfu Suzukamo
Takatsuki Research Laboratory, Sumitomo Chemical Co., Ltd.,
Takatsuki, Osaka 569, Japan



In entry 1 ~ 17 (R^1 = H or alkyl)
Benzyl cation (4) initially formed rearranges into homoallyl cation (5) through bond-A cleavage.
The (Z)-form of the homoallyl cation (5) undergoes intramolecular Friedel-Crafts reaction with the phenyl group to afford the corresponding α-Cl or α-Br naphthalenes.

In entry 18-19 (R^1 = aryl)
Benzyl cation intermediate (6) ratherthan (5) was formed due to the higher stability of the cation compared with dihalocarbinyl cation

Table 1. Synthesis of α- and β-halonaphthalenes 2 and 3 from aryl(*gem*-dihalocyclopropyl)methanols (ADCM) 1.[a)]

Entry	Substrate	X	R^1	R^2	R^3	Y_n	acid (equiv.)	Product 2 (%)	Product 3 (%)
1	1a	Cl	H	Me	H	H	$BF_3\cdot OEt_2$ (1.0)	62	0
2	1a	Cl	H	Me	H	H	$SnCl_4$ (1.0)	55	0
3	1a	Cl	H	Me	H	H	$TiCl_4$ (1.0)	35	0
4	1a	Cl	H	Me	H	H	CF_3CO_2H[b)]	77	0
5	1b	Cl	H	Me	Ph	H	$BF_3\cdot OEt_2$ (1.0)	100	0
6	1c	Cl	Me	H	Ph	H	$SnCl_4$ (1.0)	22	0
7	1c	Cl	Me	H	Ph	H	CF_3CO_2H[b)]	0	0
8	1d	Cl	Et	Me	Ph	H	$BF_3\cdot OEt_2$ (1.0)	86	0
9	1d	Cl	Et	Me	Ph	H	$SnCl_4$ (1.0)	85	0
10[c)]	1e	Cl	H	Me	H	p-MeO	$BF_3\cdot OEt_2$ (1.0)	43[d)]	0
11[c)]	1e	Cl	H	Me	H	p-MeO	CF_3CO_2H[b)]	28[d)]	0
12[c)]	1e	Cl	H	Me	H	p-MeO	$SnCl_4$ (1.0)	62[d)]	0
13[c)]	1f	Cl	H	Me	H	o-MeO	$BF_3\cdot OEt_2$ (1.0)	66[e)]	0
14[c)]	1g	Cl	H	Me	H	p-Me	$SnCl_4$ (1.0)	65[d)]	0
15[c)]	1h	Cl	H	Me	H	p-Cl	$SnCl_4$ (1.0)	27[d)]	0
16[c)]	1i	Cl	H	Me	H	p-NHAc	$SnCl_4$ (1.0)	39[d)]	0
17[c)]	1j	Br	H	Me	H	p-Me	$SnCl_4$ (1.0)	82[d)]	0
18	1k	Cl	Ph	Me	H	H	CF_3CO_2H[b)]	0	78
19	1l	Br	Ph	Me	H	H	CF_3CO_2H[b)]	0	64

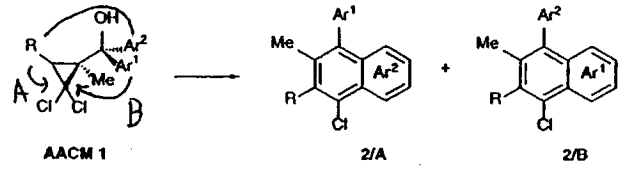
a) These reactions were carried out in 1,2-dichloroethane at room temperature for 1h~24h unless noted otherwise. b) Used as solvent. c) Diluted conditions (about 1×10^{-2} M) in the presence of molecular sieves 4A. d) 1-Halo-3-methyl-7-substituted (Y_n) naphthalenes were obtained as a sole regioisomer. e) 1-Chloro-3-methyl-5-methoxynaphthalene was obtained as a sole regioisomer.

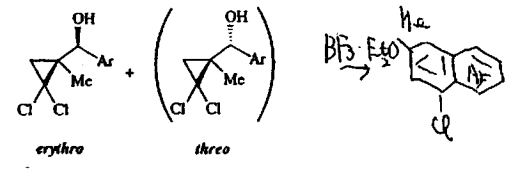
(3) Regiocontrol benzannulation

Regiocontrolled Benzannulation of Diaryl(*gem*-dichlorocyclopropyl)methanols for the Synthesis of "Unsymmetrically" Substituted α-Arylnaphthalenes

Yoshinori Nishii, Taichi Yoshida, and Yoo Tanabe*

Tetrahedron Lett. 1997. 38. 7195

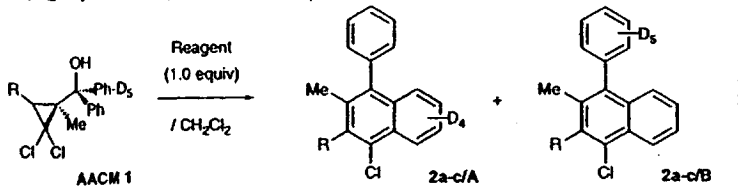




↳ Both S.M. gave same product in almost the same yield.
→ SN1' mechanism was supported!

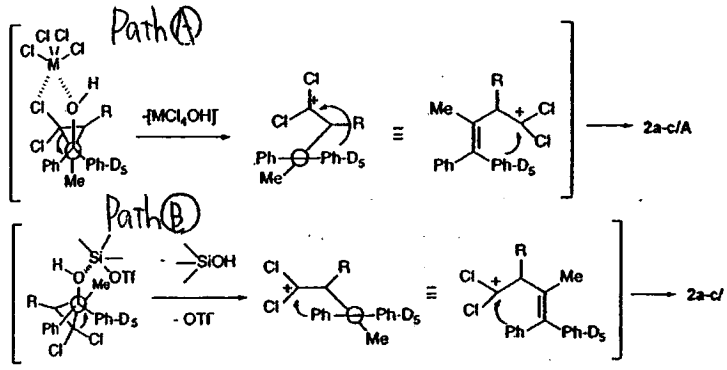
If the reaction of aryl¹ (aryl²) dichloro cyclopropyl methanol proceeds through SN1'-like cationic intermediate it might be naturally hard to differentiate the two aryl groups during the annulation

Lewis Acid Effects



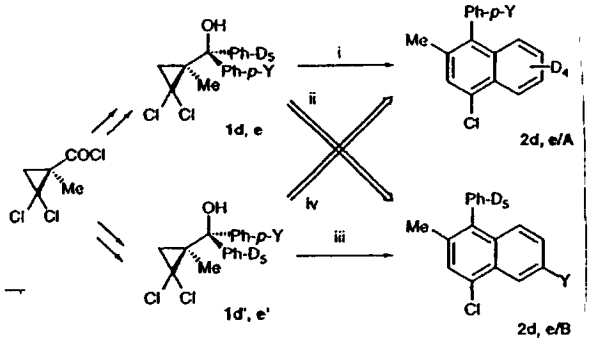
AACM	Reagent	Temp. / °C	Product	A:B[a]		Yield /%
1a	CF_3CO_2H[b]	0-5	2a	1:1.5	mix	83
	$BF_3 \cdot OEt_2$	0-5		1:1	mix	94
	$SnCl_4$	-60		3:1	A	90
	$TiCl_4$	0-5		5:1	A	38[c]
	$TiCl_4$	-60		9:1	A	91
	TMSOTf	-60		1:2	B	35[d]
	TBDMSOTf	-60		1:6	B	43[d]
	TBDMSOTf	-60		1:5	B	84[e]
1b	$TiCl_4$	-60	2b (=2a)	10:1		46[c]
	TBDMSOTf	-60		1:4		49[d]
1c	$TiCl_4$	-60	2c	9:1		81
	TBDMSOTf	-60		1:8		51[e,f]

a) These ratios were determined by ^1H NMR (400 MHz) integration values of the aromatic protons. b) CF_3CO_2H was used as solvent. c) Complex mixtures were given as by-products. d) See Ref. 7 e) The reaction was carried out in toluene solvent. The reason for an improvement of the yield is not clear at present. f) See Ref. 8.



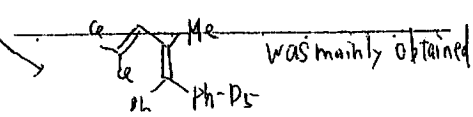
Ⓐ MCl_4 chelated both Cl and OH and regulate the conformation of Transition State

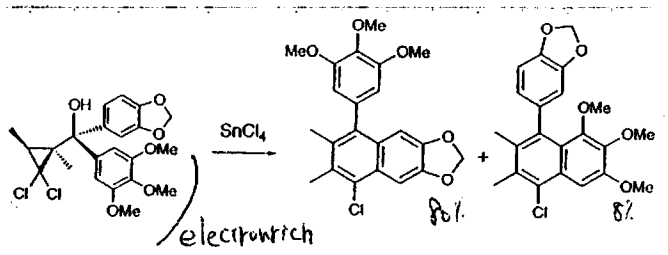
Ⓑ Silyl triflates chelated only OH and gave product B



	1d or 1d': Y=Me	1e or 1e': Y=Cl
2d	i) A:B=14:1, 52%	i) A:B=20:1, 70%
	ii) A:B=1:99, 62%	ii) trace
	iii) A:B=1:99, 40%	iii) A:B=1:4, 68%
	iv) A:B=96:4, 44%	iv) A:B=99:1, 43%

Eight crossover experiments showed desirable results except one experiment





→ The result supported chelation control decided the product.

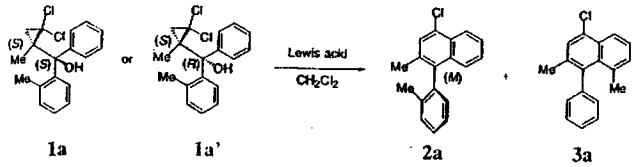
(4) Chirality exchange from sp^3 central chirality to axial chirality

Chirality Exchange from sp³ Central Chirality to Axial Chirality: Benzannulation of Optically Active Diaryl-2,2-dichlorocyclopropylmethanols to Axially Chiral α-Arylnaphthalenes

Yoshinori Nishii,* Kazunori Wakasugi,† Keisuke Koga,† and Yoo Tanabe*,†

J. Am. Chem. Soc. 2004, 126, 5358

Table 1. Chirality Exchange Benzannulation of AACM **1a** and **1a'**

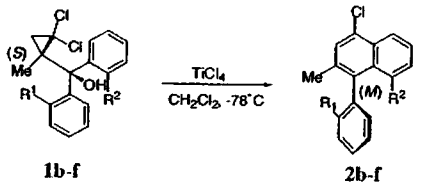


1a **1a'** **2a** **3a**

entry	substrate[a]	Lewis acid[b]	T (°C)	yield (%)[c]	ratio[d] (2a:3a)	ee of 2a (%)[e]
1	1a	$TiCl_4$	0	75	(74:26)	97
2	1a	$TiCl_4$	−78	96	(>99:1)	>99
3	1a	$SnCl_4$	−78	72	(>99:1)	>99
4	1a'	$TiCl_4$	−78	89	(>1:99)	–
5	1a'	TBDMSOTf	0	41	(97:3)	45
6	1a'	TMSOTf	0	54	(77:23)	55
7	1a'	TBDMSOTf	−78	trace	–	–

[a] Optical purities: >99% ee. [b] 1.0 equiv of Lewis acid was used. [c] Isolated yields. [d] Determined by ^1H NMR. [e] Determined by HPLC with a Chiralcel OD column.

Table 2. Chirality Exchange Benzannulation of AACMs **1b–f** Using $TiCl_4$ [a]

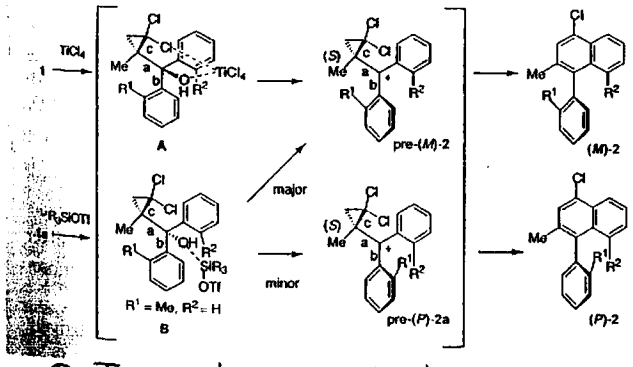


1b-f **2b-f**

entry	substrate[b]	R^1	R^2	product	yield (%)[c]	ee (%)[d]
1	**1b**	Cl	H	**2b**	97	>99
2	**1c**	Cl	Cl	**2c**	70	>99
3	**1d**	MeO	Me	**2d**	71	>99
4	**1e**	MeO	Cl	**2e**	65	>99
5	**1f**	Me	Cl	**2f**	47	>99

[a] 1.0 equiv of $TiCl_4$ was used. [b] Optical purity of each AACM was >99% ee. [c] Isolated yields. [d] Determined by HPLC with a Chiralcel OD column.

Scheme 1



① $TiCl_4$ chelates with the oxygen and chlorine of 1 to give intermediate A. The ortho substituent (R') turned to the backside of the chelation face.

② The cationic intermediate pre-(M)-2 was given by elimination of OH group promoted by $TiCl_4$

③ The conjugation between the cyclopropyl methyl cation and bromatic ring (Ar) prevent the free rotation of bond b of pre-(M)-2

④ Highly regioselective ring-opening of bond C and Friedel-Crafts-type cyclization occured.