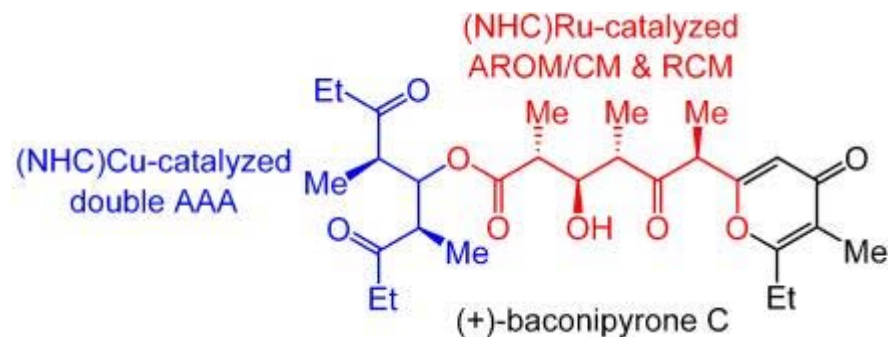


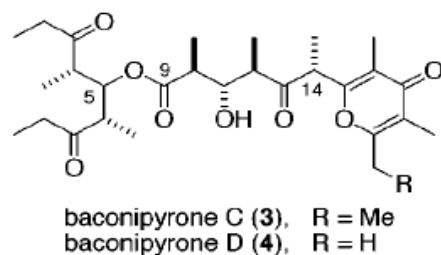
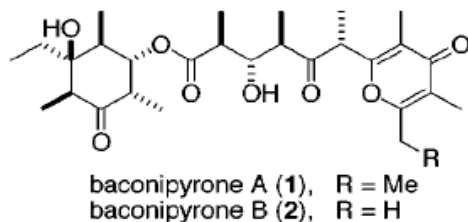
Chiral N-Heterocyclic Carbenes in Natural Product Synthesis: Application of Ru-Catalyzed Asymmetric Ring-Opening/Cross-Metathesis and Cu-Catalyzed Allylic Alkylation to Total Synthesis of Baconipyrrone C



Dennis G. Gillingham and Amir H. Hoveyda
Angew. Chem. Int. Ed. 2007, Early View

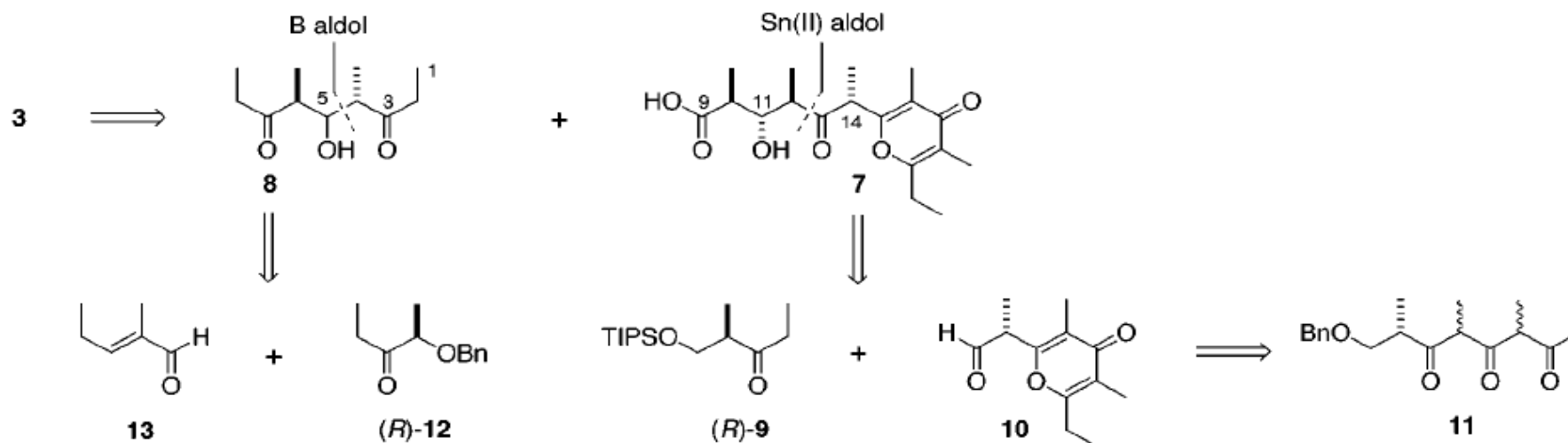
Current Literature
Chenbo Wang @ Wipf Group
May 12th, 2007

Baconipyrones

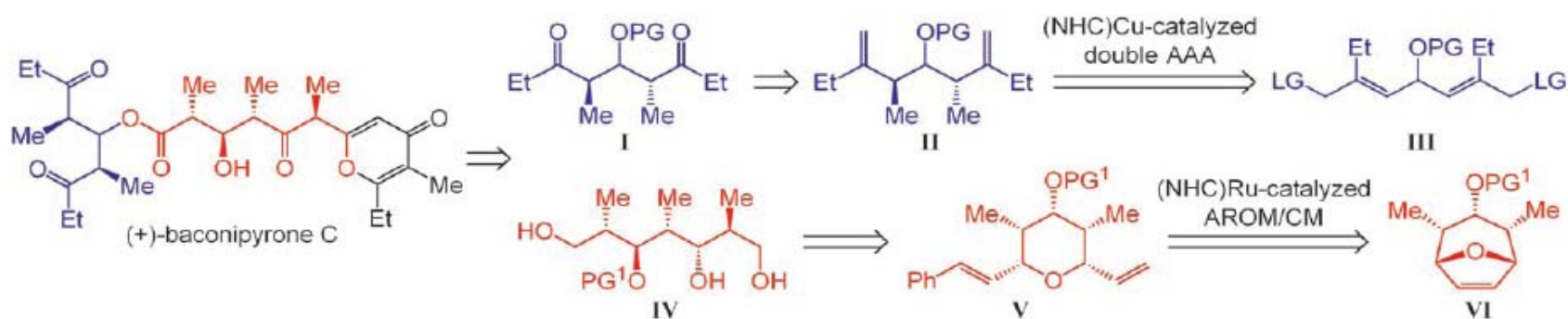


- Baconipyrones A-D (1-4) were isolated from *Siphonaria baconi* collected from intertidal rock platforms near Melbourne, Australia.
- No biological activity was reported.
- Its first total synthesis was reported in 2000 by Paterson group.

Paterson's retro synthesis:

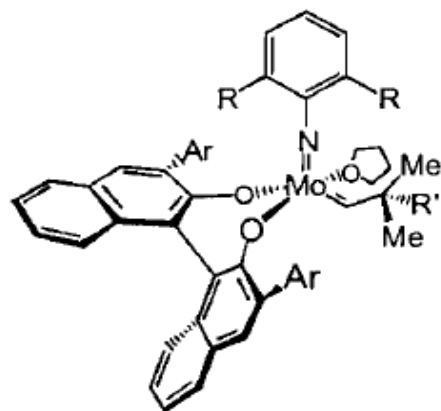


Hoveyda's Retrosynthetic Analysis for Baconipyronone C

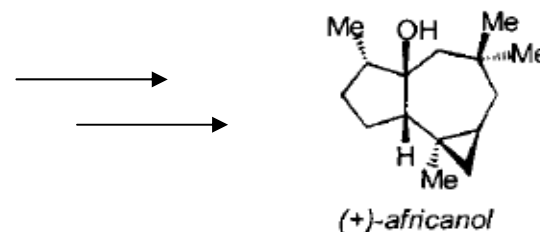
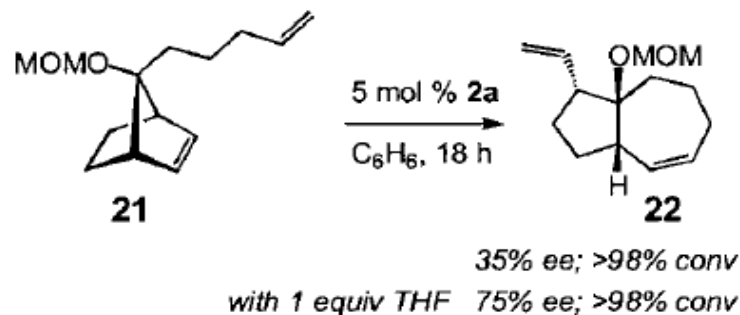


Scheme 2. Retrosynthetic analysis for baconipyronone C. AAA = asymmetric allylic alkylation; AROM/CM = asymmetric ring-opening/cross-metathesis; PG = protecting group; LG = leaving group.

Mo-catalyzed Asymmetric Metathesis: ROM-RCM



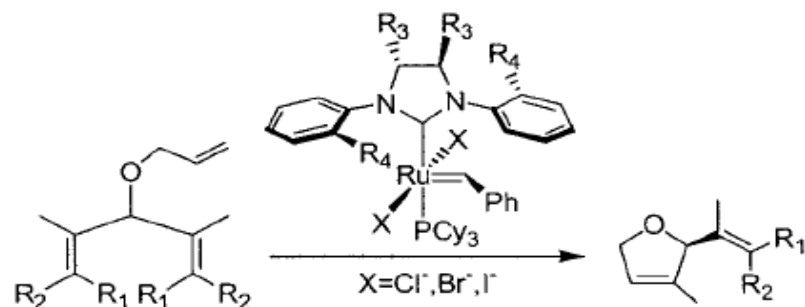
2a R = *i*-Pr R' = Ph
2b R = Me R' = Ph
2c R = Cl R' = Me
Ar = 2,4,6-(*i*-Pr)₃C₆H₃



- Chiral Mo-based catalysts effect asymmetric asymmetric ring-opening metathesis (AROM)/ring-closing metathesis
- Catalyst **2a** was applied to (+)-africanol synthesis via desymmetrization of the starting material **21**
- Mo-based Catalysts have stability issues and polymerization process often competes

Weatherhead, G. S.; Cortez, G. A.; Schrock, R. R. and Hoveyda, A. H. *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5805

Ru-catalyzed Asymmetric Metathesis: Grubbs II based catalyst, 1st Generation, RCM



Proposed Stereochemical model:

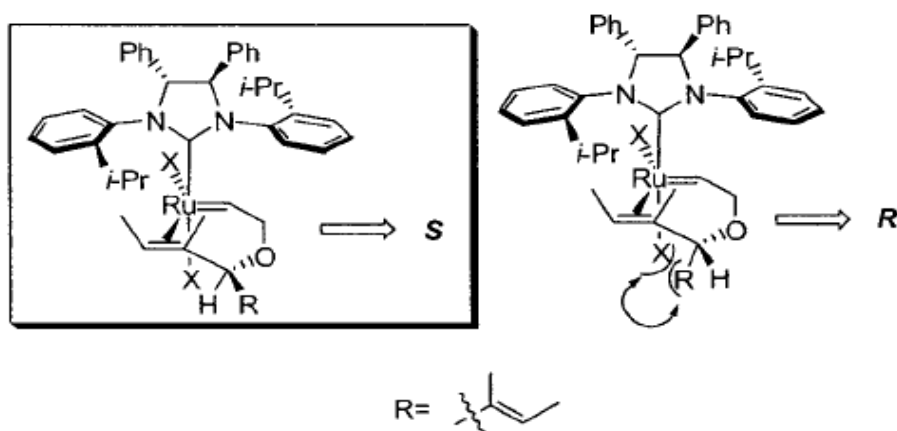
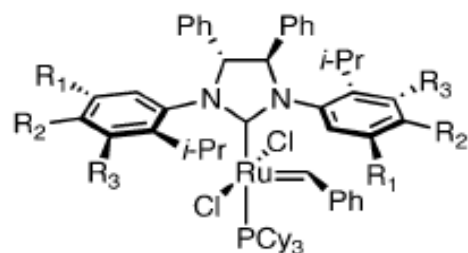


Table 1. Enantioselective Desymmetrization of Trienes 10–12 by Catalysts 8a–c

entry	substrate	catalyst	product	ee(%) ^b	k_{rel}	convn(%) ^c
1		8a		13	1.3	57
2		8b		23	1.6	95
3		8c		23	1.6	96
4		8b+Nal		38	2.2	18
5	10	8c+Nal	(S)-13	39	2.2	20
6		8b+Nal		17	1.4	78
7		8c+Nal	(S)-14	35	2.1	90
8		8b+LiBr		63	4.4	90
9		8b+Nal		85	12.3	91
10		8c+LiBr		69	5.5	90
11	12	8c+Nal	(S)-15	90	19	82

Seiders, T. J.; Ward, D. W. and Grubbs, R. H. *Org. Lett.* **2001**, 3, 3225

Ru-catalyzed Asymmetric Metathesis: Grubbs II based catalyst, 2nd Generation, RCM



2a ($R_1, R_2, R_3 = H$),
2b ($X = I$)

3a ($R_1 = i\text{-Pr}; R_2, R_3 = H$),

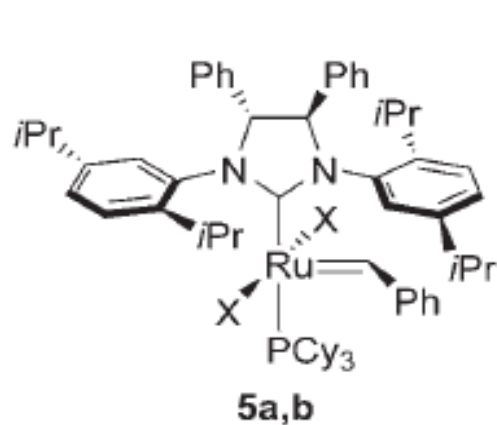
4a ($R_1 = t\text{-Bu}; R_2 = \text{OMe}; R_3 = H$),

5a ($R_1, R_2 = H; R_3 = i\text{-Pr}$),

triene	product	catalyst (mol %)	ee (%) ^b	conversion (%) ^c	yield (%)
		2b (4)	90	>98	64
11	12				
		5a (0.8)	92	>98	77'
13	14				
		2b (4)	90	>98	77
15	16				
		2b (4)	85	5	nd
17	18	5a (2) ^d	76	93	92
		2b (4)	85	~2 ^e	nd
19	20				
		5a (1)	92	65	64
21	22				
		2b (4)	78	>98	98
23	24				

Funk, T. W.; Berlin, J. M. and Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 1840

Ru-catalyzed Asymmetric Metathesis: Grubbs II based catalyst, 2nd Generation, CM



a: X=Cl, b: X=I

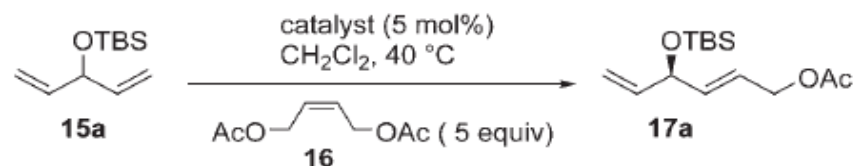
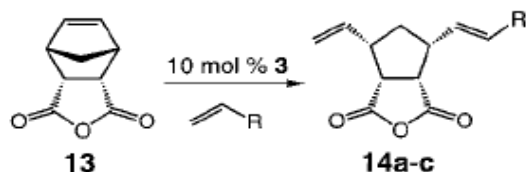
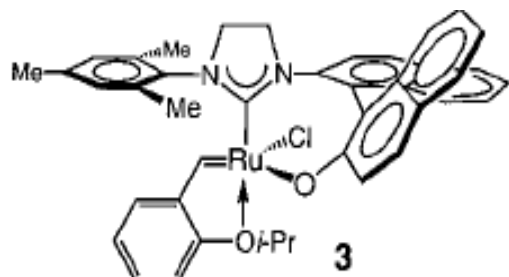


Table 4: ACM with *cis*-1,4-diacetoxy-2-butene using catalyst **5a**.

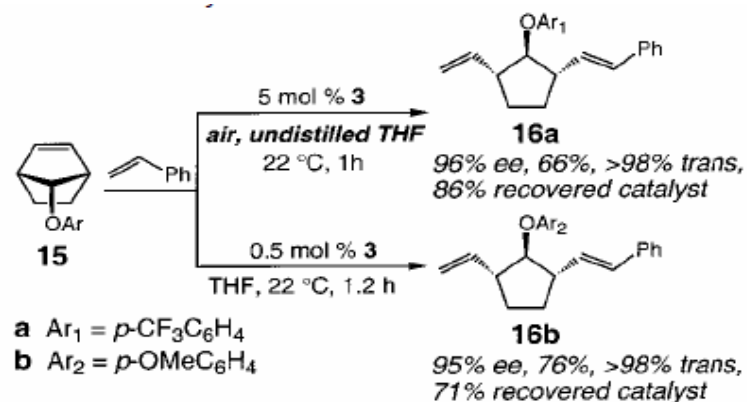
Substrate	Product	<i>ee</i> [%]	Yield [%]
		52	54 ^[a]
		40	17 ^[b]
		37	48 ^[c]
	—	n.r.	n.r.
		4	23 ^[c]

[a] 5 mol % **5a**, 5 equiv of **15b** relative to **16**, no solvent, 40 °C, 6 h. [b] 5 mol % **5a**, 5 equiv of **16**, no solvent, 40 °C, 6 h. [c] 5 mol % **5a**, 5 equiv of **16**, 0.25 M in CH₂Cl₂, 40 °C, 6 h. TIPS = triisopropylsilyl, TMS = trimethylsilyl, n.r. = no reaction.

Ru-catalyzed Asymmetric Metathesis: Hoveyda-Grubbs II based catalyst, 1st Generation, ROM-CM

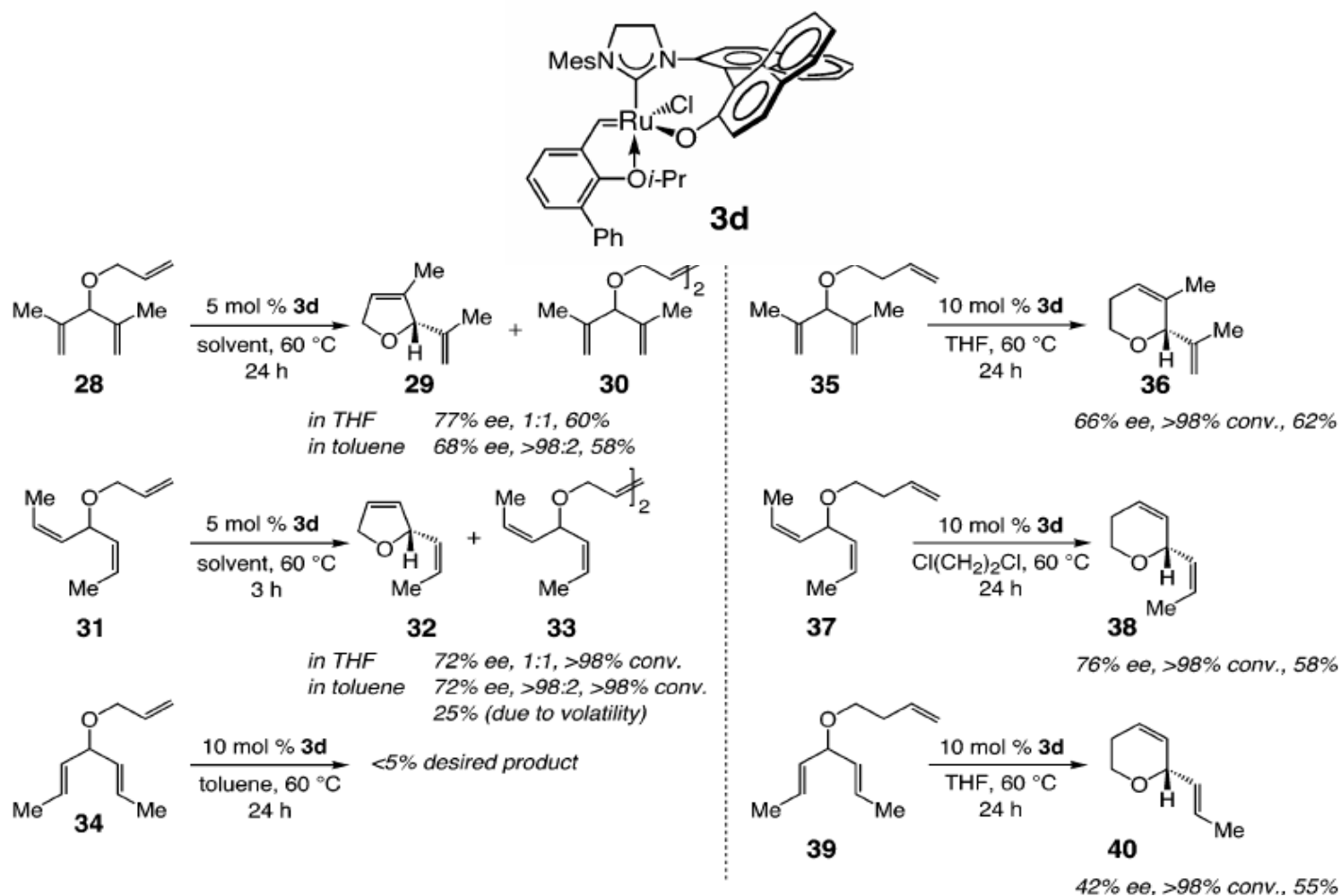


entry	R		temp (°C); time (h)	conv (%) ^b ; yield (%) ^c	recov. cat. (%) ^c	trans:cis ^b	ee (%) ^d
1	Ph	a	50; 1.0	>98; 71	96	>98: 2	80
2	<i>n</i> -C ₅ H ₁₁	b	50; 1.5	>98; 57	92	>98: 2	>98
3	Cy	c	50; 1.0	>98; 60	88	>98: 2	>98



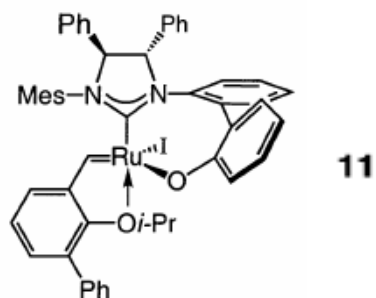
van Veldhuizen, J. J.; Kingsbury, J. S.; Garber, S. B. and Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 4954

Ru-catalyzed Asymmetric Metathesis: Hoveyda-Grubbs II based catalyst, 2nd Generation, RCM



Van Veldhuizen, J. J.; Gillingham, D. G.; Garber, S. B.; Kataoka, O. and Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 12502

Ru-catalyzed Asymmetric Metathesis: Hoveyda-Grubbs II based catalyst, 3rd Generation, ROM-CM

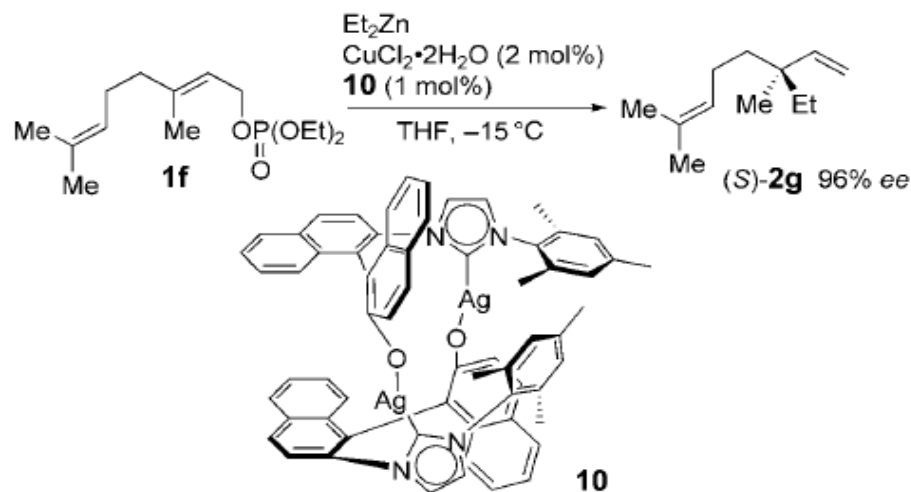


entry	substrate	product	<i>in situ</i> complex 10 conv (%); ^b t (h), yield (%); ^c ee (%) ^d	complex 1b conv (%); ^b t (h), yield (%); ^c ee (%) ^d	<i>in situ</i> complex 11 conv (%); ^b t (h), yield (%); ^c ee (%) ^d	complex 11 conv (%); ^b t (h), yield (%); ^c ee (%) ^d	complex 1c conv (%); ^b t (h), yield (%); ^c ee (%) ^d
1			>98; 0.1 59; 84	>98; 0.3 60; 70	>98; 2 62; 89	>98; 2 50; 90	>98; 4 72; >98
2			>98; 0.5 82; 74	>98; 1.5 80; 94	>98; 0.5 89; >98	>98; 1 71; 93	>98; 2 81; 97
3			>98; 1 84; 71	50; 48 66; 67	>98; 1 87; 83	>98; 1.5 73; 84	<2; 48
4 ^e			>98; 1 57; 84	>98; 1 20; 46	>98; 1 66; 93	>98; 1 52; 90	>98; 1 71; 43

^a Reactions carried out with 5 mol % Ru catalyst in THF (except entry 3 performed in the absence of solvent) in the presence of 5 equiv of styrene at 22 °C. See the Supporting Information for detailed conditions. ^b Conversions determined by analysis of 400 MHz ¹H NMR spectra of unpurified product mixtures. ^c Isolated yield after silica gel chromatography. ^d Enantioselectivities determined by chiral HPLC (see the Supporting Information for details). ^e Reaction performed through slow addition of substrate to a solution of the catalyst and styrene in THF.

10

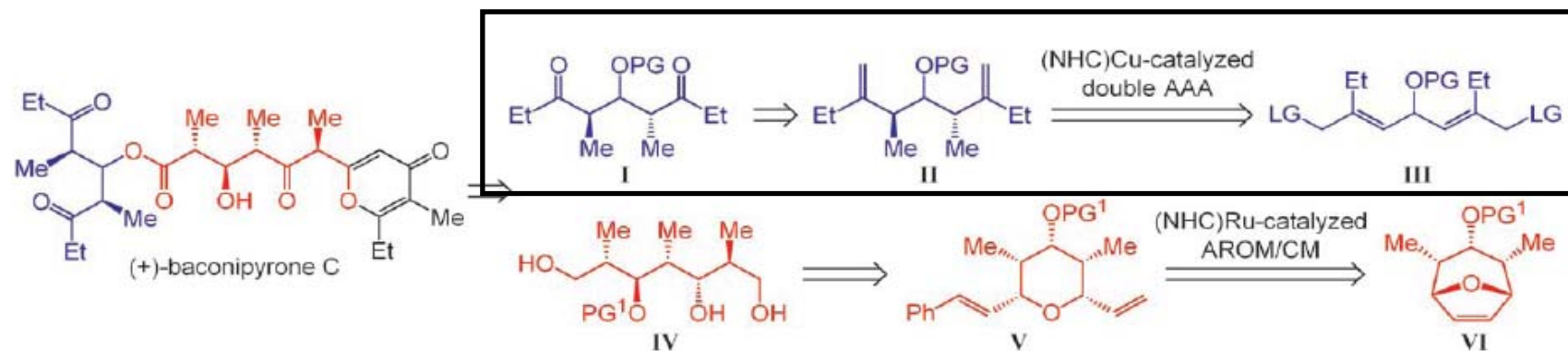
Cu-Catalyzed Asymmetric Allylic Alkylation (AAA)



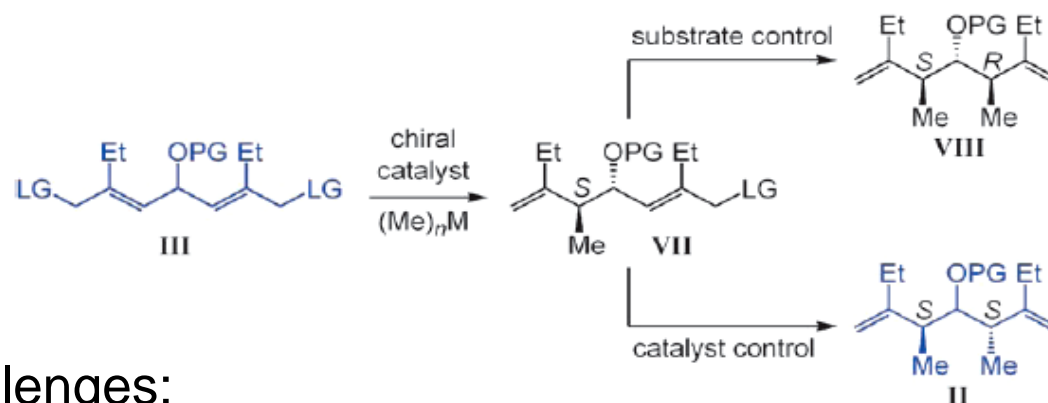
- Cu-catalyzed allylic alkylation allows the use of hard nucleophiles (RMgX , R_2Zn) with high $\text{S}_{\text{N}}2'$ regioselectivity.
- The asymmetric version has emerged recently.

Larsen, A. O.; Leu, W.; Oberhuber, C. N.; Campbell, J. E. and Hoveyda A. H., *J. Am. Chem. Soc.* **2004**, *126*, 11130

Synthesis of Baconipyronone D: Left Hand Fragment by AAA



Scheme 2. Retrosynthetic analysis for baconipyronone C. AAA = asymmetric allylic alkylation; AROM/CM = asymmetric ring-opening/cross-metathesis; PG = protecting group; LG = leaving group.

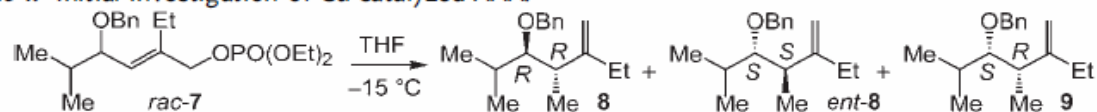


The challenges:

- Steric congested trisubstituted olefin
- S_N2 vs. S_N2'
- Substrate control vs. catalyst control in the second AAA

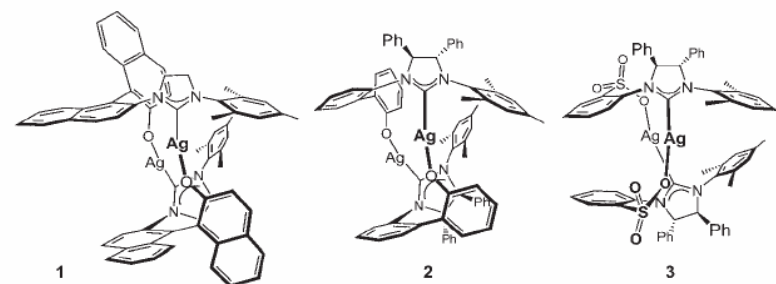
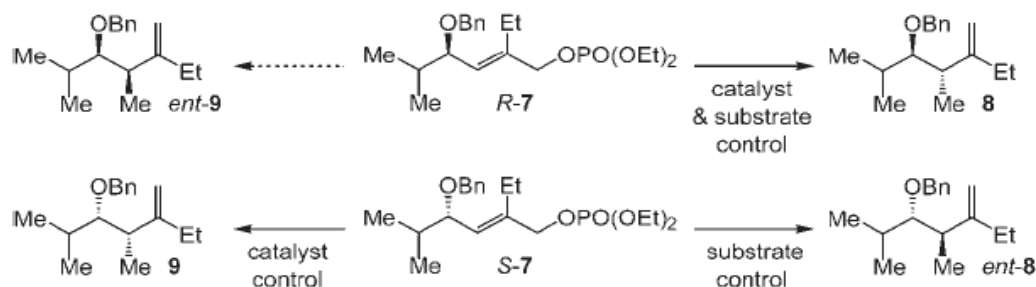
Left Hand Fragment: Model Study

Table 1: Initial investigation of Cu-catalyzed AAA.^[a]

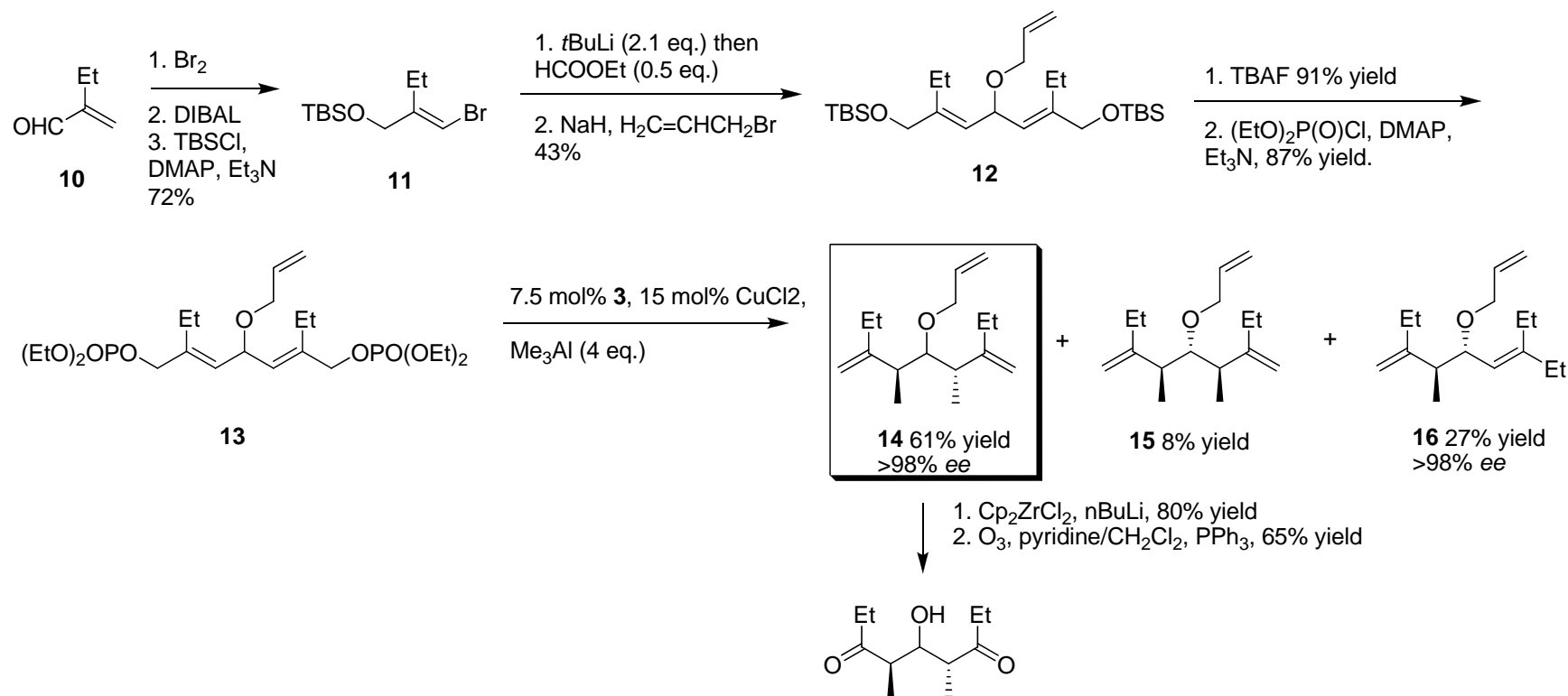


Entry	Alkyl metal	Catalyst (mol%)	Conv. [%] ^[b]	t [h]	S _N 2':S _N 2 ^[b]	8:9 ^[b]	e.r. [%] 8 ^[c]	ee [%] 8 ^[c]
1	Me ₂ Zn	CuCN (200)	10	24	> 20:1	9:1	–	–
2	Me ₂ Zn	1 (7.5); CuCl ₂ ·2H ₂ O (15)	< 2	24	–	–	–	–
3	Me ₂ Zn	2 (7.5); CuCl ₂ ·2H ₂ O (15)	< 2	24	–	–	–	–
4	Me ₂ Zn	3 (7.5); CuCl ₂ ·2H ₂ O (15)	< 2	24	–	–	–	–
5	Me ₃ Al	CuCN (15)	> 98	4	> 20:1	9:1	–	–
6	Me ₃ Al	1 (7.5); CuCl ₂ ·2H ₂ O (15)	45	24	> 20:1	20:1	99:01	98
7	Me ₃ Al	2 (7.5); CuCl ₂ ·2H ₂ O (15)	15	24	nd	9:1	nd	nd
8	Me ₃ Al	3 (7.5); CuCl ₂ ·2H ₂ O (15)	68	1	> 20:1	2.6:1	97:03	94
9	Me ₃ Al	3 (7.5); CuCl ₂ ·2H ₂ O (15)	89	4.5	> 20:1	1.7:1	95:05	90
10	Me ₃ Al	3 (7.5); CuCl ₂ ·2H ₂ O (15)	95	24	> 20:1	1.5:1	94.5:5.5	89

[a] Reactions were performed under N₂. [b] Determined by 400-MHz ¹H NMR analyses of unpurified mixtures. [c] Determined by chiral GLC analysis (see the Supporting Information for details). nd = not determined.

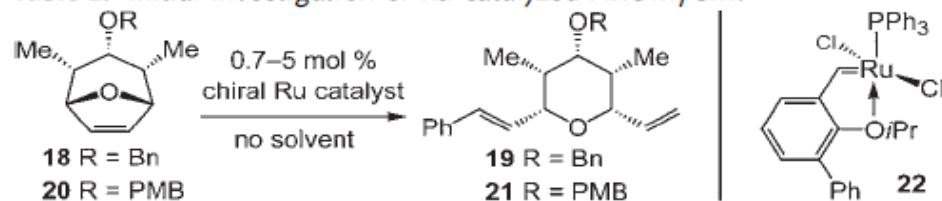


Left Hand Fragment: Synthesis



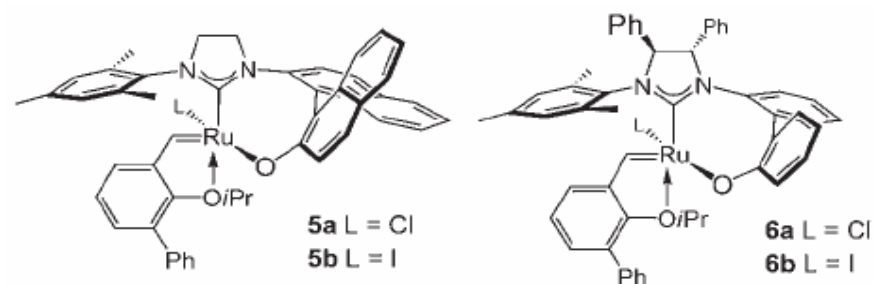
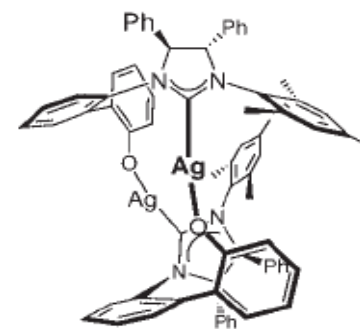
Right Hand Fragment: AROM/CM

Table 2: Initial investigation of Ru-catalyzed AROM/CM.^[a]

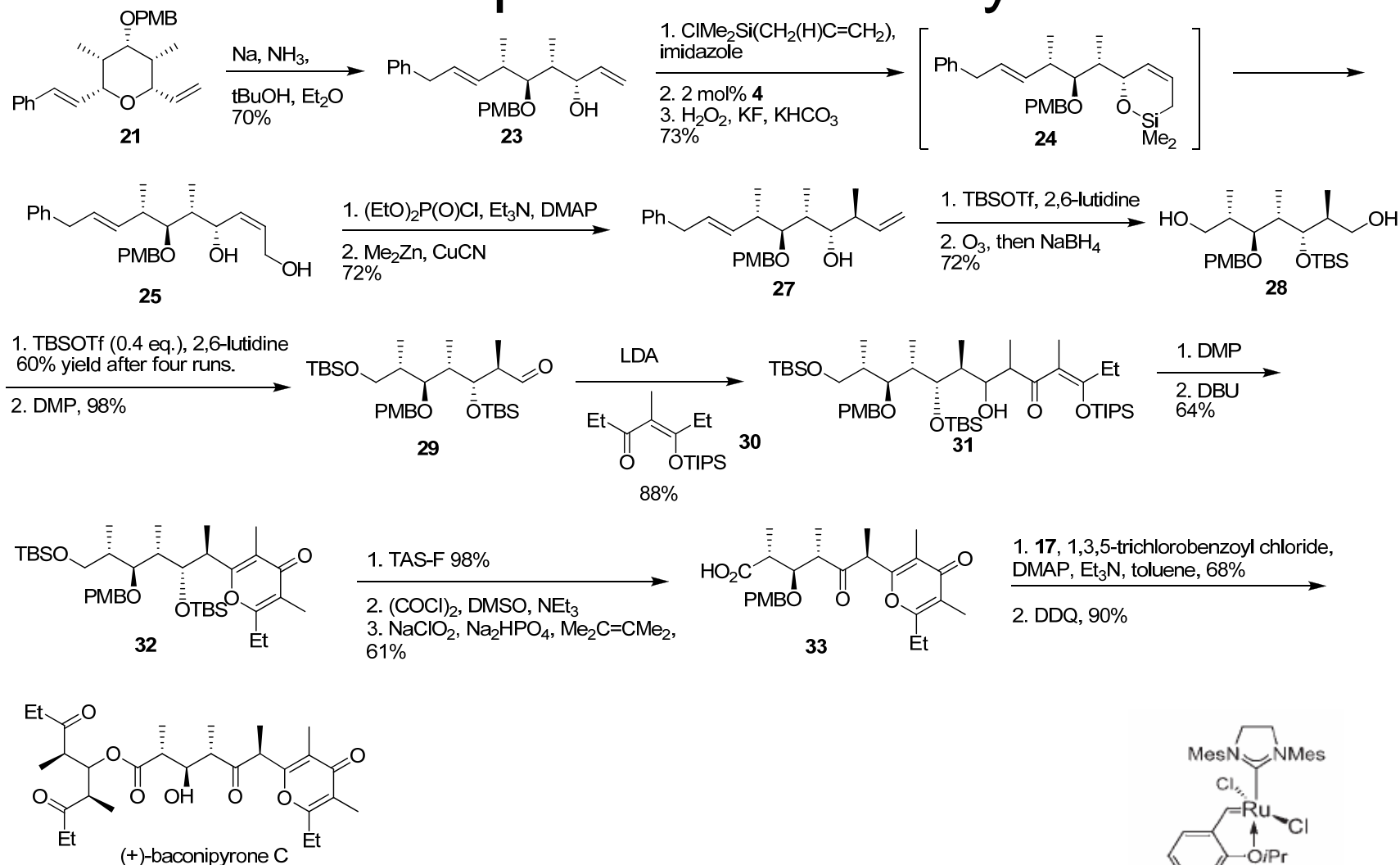


Entry	Substrate	Catalyst (mol %)	Equiv styrene	T [°C]; t [h]	Conv. [%] ^[b] ; Yield [%] ^[c]	ee [%] ^[d]
1	18	5b (5)	4	22; 44	96; 55	80
2	18	6b (5)	4	22; 15	>98; 56	81
3	18	2 + 22 + NaI (2.5)	4	22; 14	>98; 44	81
4	18	2 + 22 + NaI (0.7)	4	22; 14	>98; 46	73
5	18	2 + 22 + NaI (2.0)	8	-15; 20	>98; 64	89
6	20	2 + 22 + NaI (2.0)	8	-15; 20	>98; 62	88

[a] Reactions were performed under N₂. [b] Conversions were determined by 400-MHz ¹H NMR analyses of unpurified mixtures. [c] Yields of isolated product after purification. [d] Determined by chiral HPLC analysis (see the Supporting Information for details).



Preparation of The Right Hand Fragment And Completion of The Synthesis



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Summary

- (+)-Baconipyrrone D was synthesized in 17 linear steps with a total yield of 2.1%.
- Key steps include Ru-catalyzed asymmetric ring-opening/cross-metathesis and Cu-catalyzed allylic alkylation, both utilizing the newly developed chiral N-heterocyclic carbene ligands.