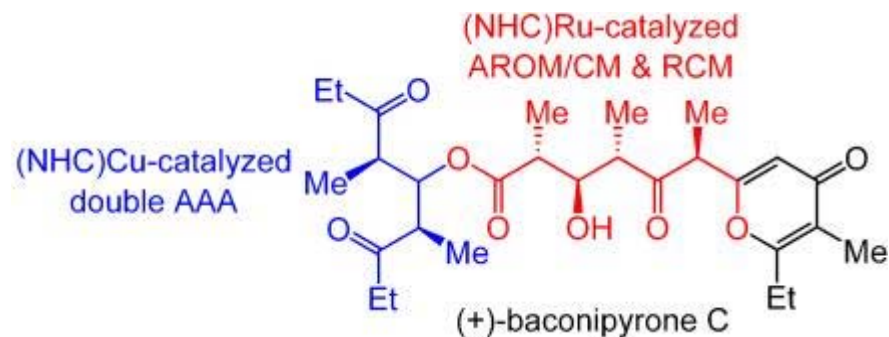


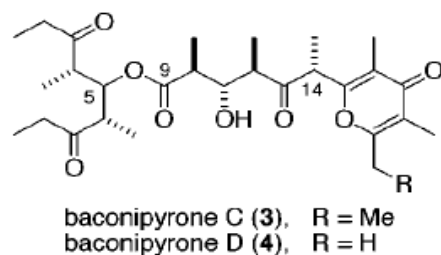
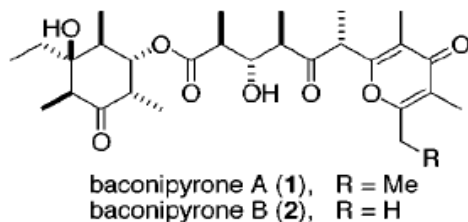
# Chiral N-Heterocyclic Carbenes in Natural Product Synthesis: Application of Ru-Catalyzed Asymmetric Ring-Opening/Cross-Metathesis and Cu-Catalyzed Allylic Alkylation to Total Synthesis of Baconipyrrone C



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

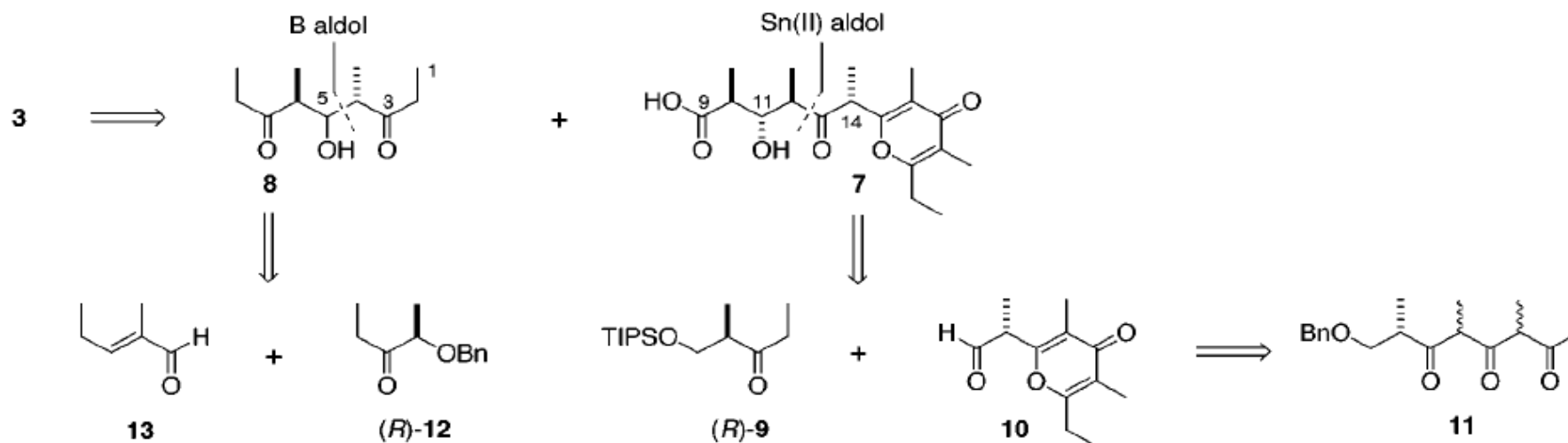
Current Literature  
Chenbo Wang @ Wipf Group  
May 12th, 2007

# Baconipyrones

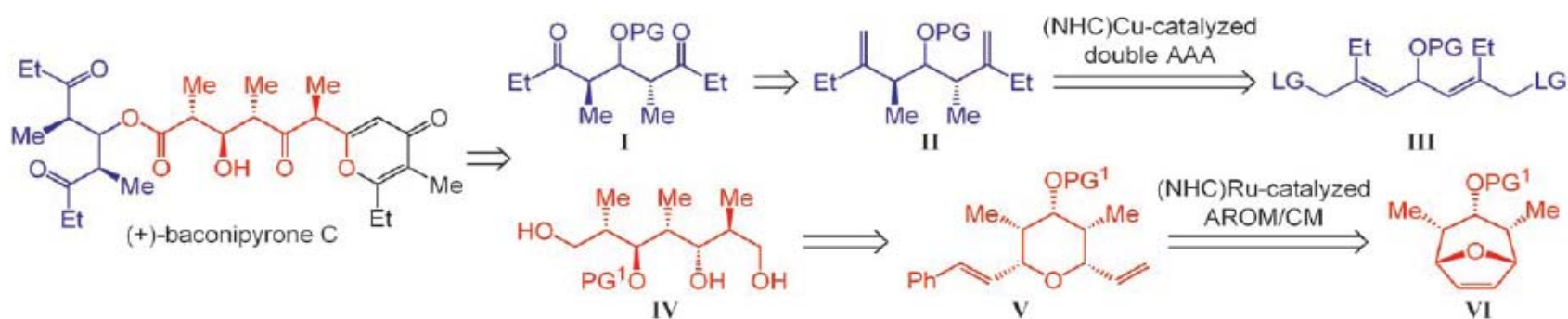


- Baconipyrones A-D (1-4) were isolated from *Siphonaria baconi* collected from intertidal rock platforms near Melbourne, Australia.
- No biological activity was reported.
- Its first total synthesis was reported in 2000 by Paterson group.

## Paterson's retro synthesis:

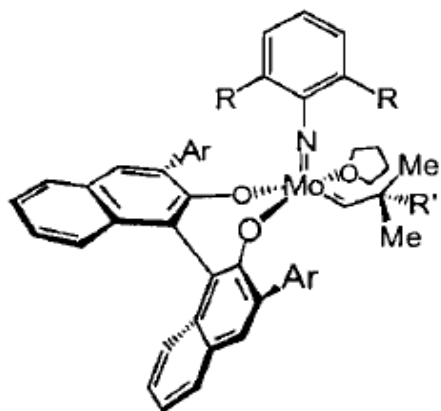


# Hoveyda's Retrosynthetic Analysis for Baconipyronone C

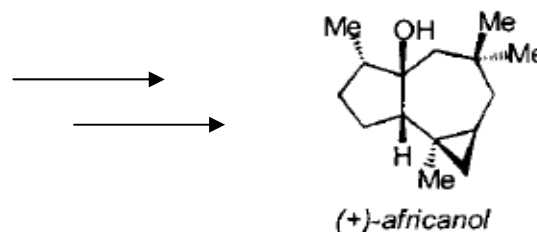
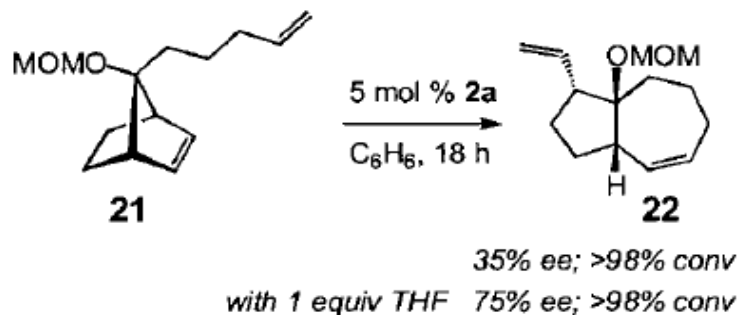


**Scheme 2.** Retrosynthetic analysis for baconipyronone C. AAA = asymmetric allylic alkylation; AROM/CM = asymmetric ring-opening/cross-metathesis; PG = protecting group; LG = leaving group.

# Mo-catalyzed Asymmetric Metathesis: ROM-RCM

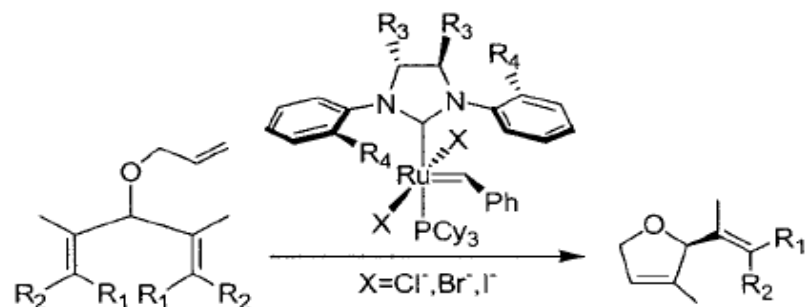


**2a** R = *i*-Pr R' = Ph  
**2b** R = Me R' = Ph  
**2c** R = Cl R' = Me  
 Ar = 2,4,6-(*i*-Pr)<sub>3</sub>C<sub>6</sub>H<sub>3</sub>

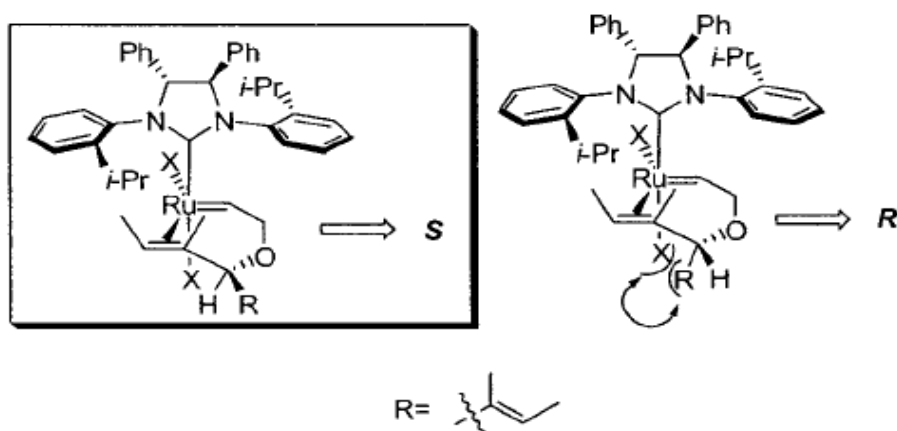


- Chiral Mo-based catalysts effect asymmetric asymmetric ring-opening metathesis (AROM)/ring-closing metathesis
- Catalyst **2a** was applied to (+)-africanol synthesis via desymmetrization of the starting material **21**
- Mo-based Catalysts have stability issues and polymerization process often competes

# Ru-catalyzed Asymmetric Metathesis: Grubbs II based catalyst, 1<sup>st</sup> Generation, RCM



Proposed Stereochemical model:

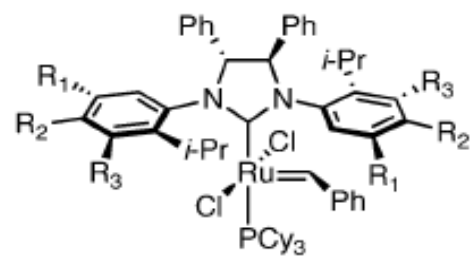


**Table 1.** Enantioselective Desymmetrization of Trienes 10–12 by Catalysts 8a–c

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

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

# Ru-catalyzed Asymmetric Metathesis: Grubbs II based catalyst, 2<sup>nd</sup> Generation, RCM



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

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

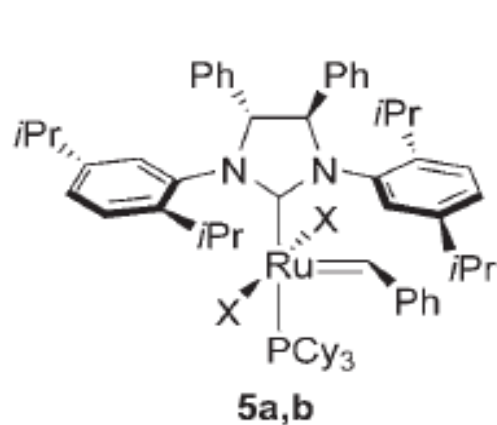
**4a** ( $R_1 = t\text{-Bu}; R_2 = \text{OMe}; R_3 = H$ ),

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

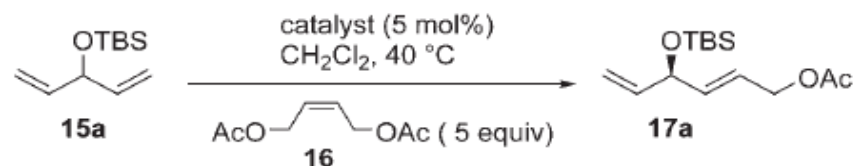
triene	product	catalyst (mol %)	ee (%) <sup>b</sup>	conversion (%) <sup>c</sup>	yield (%)
		<b>2b</b> (4)	90	>98	64
<b>11</b>	<b>12</b>				
		<b>5a</b> (0.8)	92	>98	77'
<b>13</b>	<b>14</b>				
		<b>2b</b> (4)	90	>98	77
<b>15</b>	<b>16</b>				
		<b>2b</b> (4)	85	5	nd
<b>17</b>	<b>18</b>	<b>5a</b> (2)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

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, 2<sup>nd</sup> Generation, CM



a: X=Cl, b: X=I

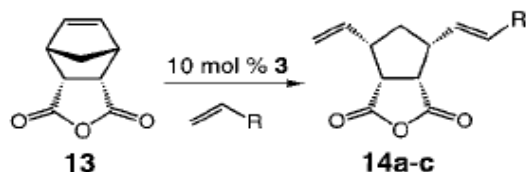
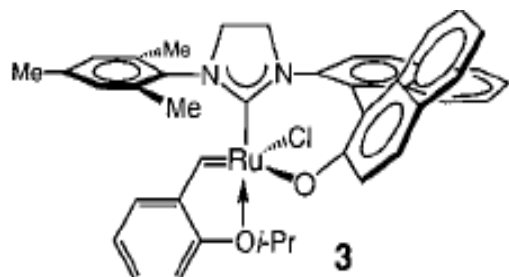


**Table 4:** ACM with *cis*-1,4-diacetoxy-2-butene using catalyst **5a**.

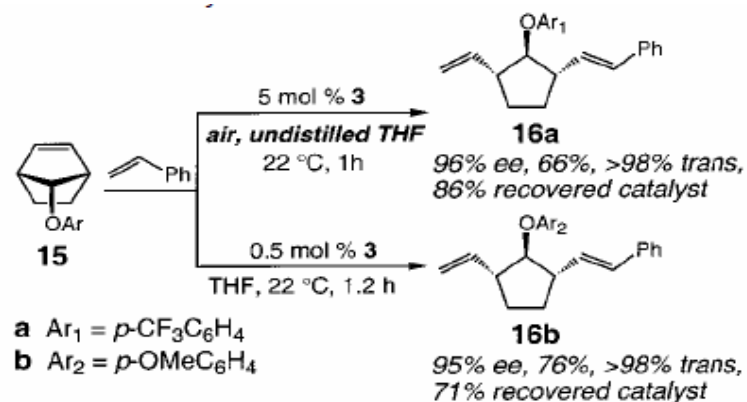
Substrate	Product	<i>ee</i> [%]	Yield [%]
		52	54 <sup>[a]</sup>
		40	17 <sup>[b]</sup>
		37	48 <sup>[c]</sup>
	—	n.r.	n.r.
		4	23 <sup>[c]</sup>

[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 CH<sub>2</sub>Cl<sub>2</sub>, 40 °C, 6 h. TIPS = triisopropylsilyl, TMS = trimethylsilyl, n.r. = no reaction.

# Ru-catalyzed Asymmetric Metathesis: Hoveyda-Grubbs II based catalyst, 1<sup>st</sup> Generation, ROM-CM

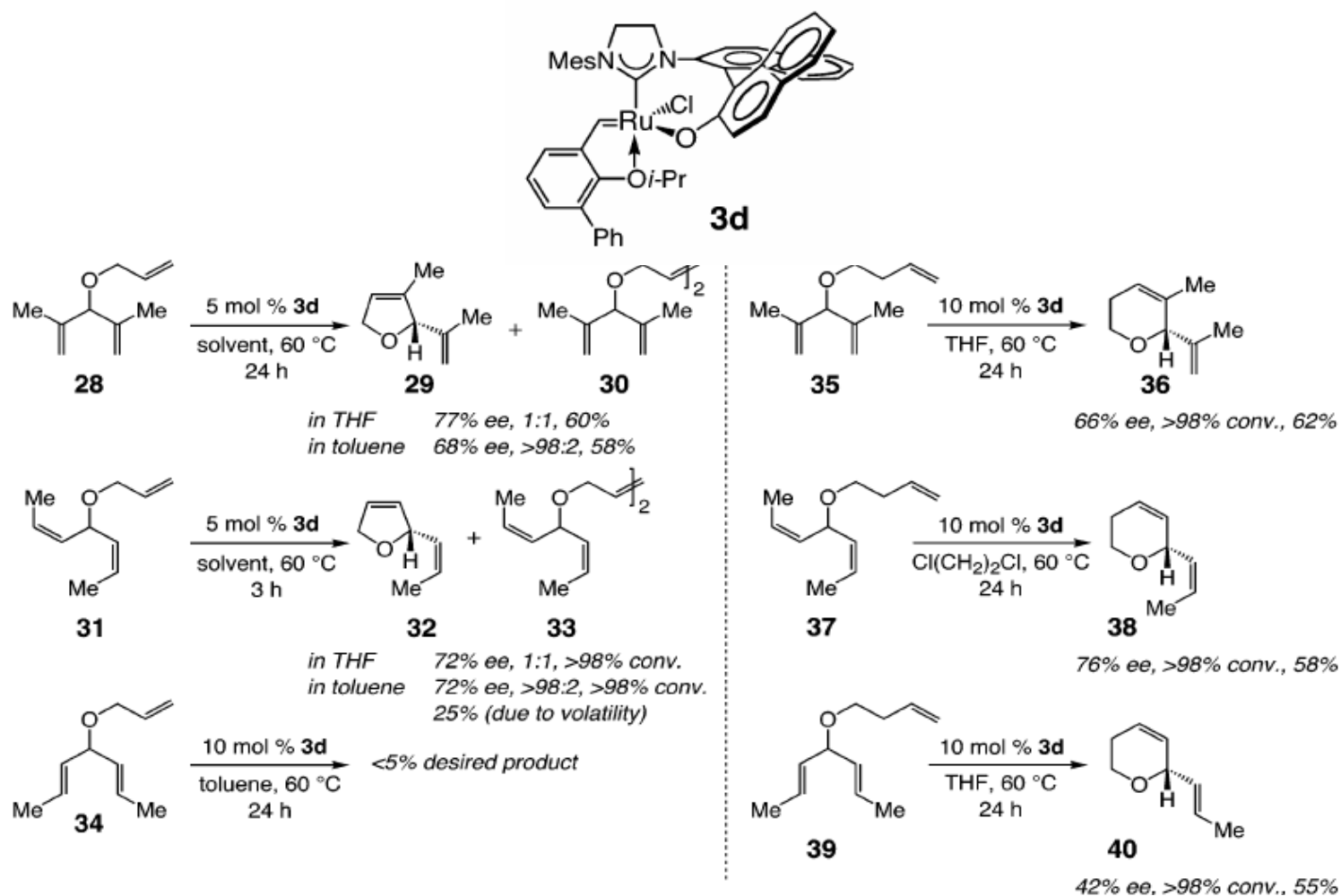


entry	R		temp (°C); time (h)	conv (%) <sup>b</sup> ; yield (%) <sup>c</sup>	recov. cat. (%) <sup>c</sup>	trans:cis <sup>b</sup>	ee (%) <sup>d</sup>
1	Ph	a	50; 1.0	>98; 71	96	>98: 2	80
2	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	b	50; 1.5	>98; 57	92	>98: 2	>98
3	Cy	c	50; 1.0	>98; 60	88	>98: 2	>98



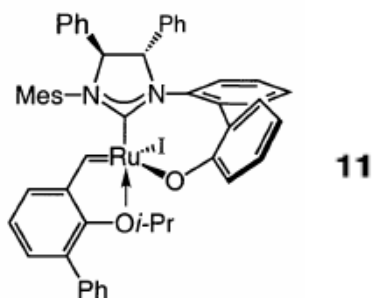


# Ru-catalyzed Asymmetric Metathesis: Hoveyda-Grubbs II based catalyst, 2<sup>nd</sup> Generation, RCM



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, 3<sup>rd</sup> Generation, ROM-CM

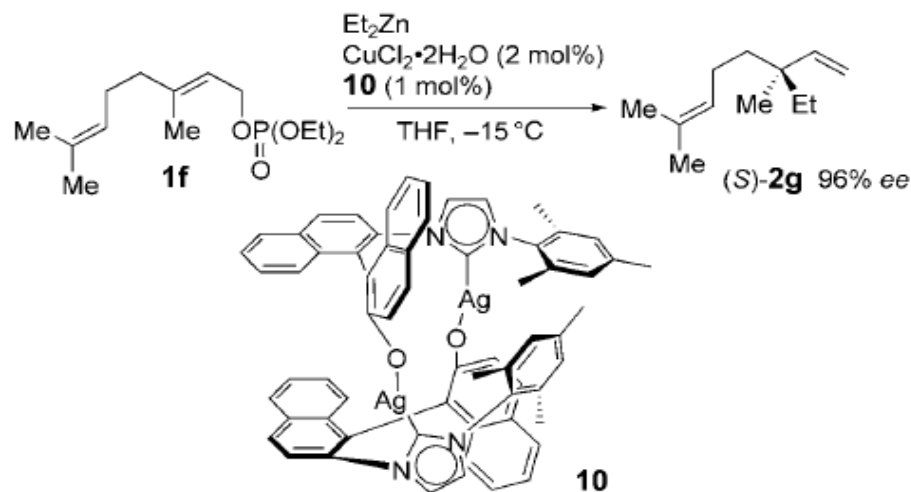


entry	substrate	product	<i>in situ</i> complex <b>10</b> conv (%); <sup>b</sup> t (h), yield (%); <sup>c</sup> ee (%) <sup>d</sup>	complex <b>1b</b> conv (%); <sup>b</sup> t (h), yield (%); <sup>c</sup> ee (%) <sup>d</sup>	<i>in situ</i> complex <b>11</b> conv (%); <sup>b</sup> t (h), yield (%); <sup>c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

<sup>a</sup> 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. <sup>b</sup> Conversions determined by analysis of 400 MHz <sup>1</sup>H NMR spectra of unpurified product mixtures. <sup>c</sup> Isolated yield after silica gel chromatography. <sup>d</sup> Enantioselectivities determined by chiral HPLC (see the Supporting Information for details). <sup>e</sup> Reaction performed through slow addition of substrate to a solution of the catalyst and styrene in THF.

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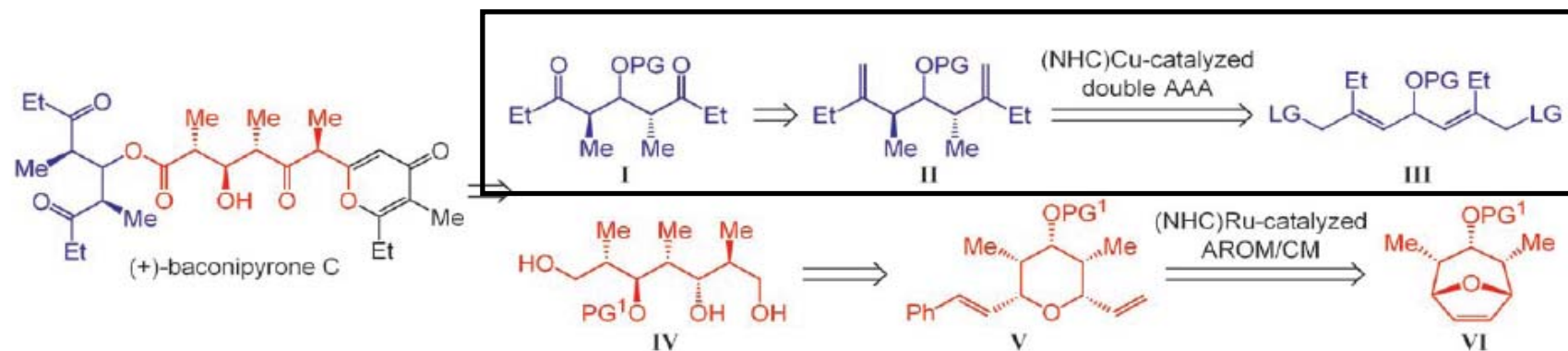
# Cu-Catalyzed Asymmetric Allylic Alkylation (AAA)



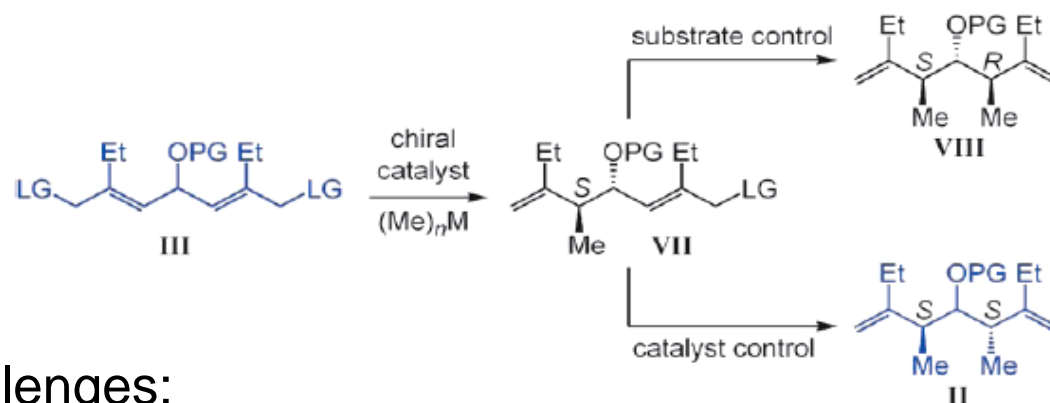
- Cu-catalyzed allylic alkylation allows the use of hard nucleophiles ( $\text{RMgX}$ ,  $\text{R}_2\text{Zn}$ ) with high  $\text{S}_{\text{N}}2'$  regioselectivity.
- The asymmetric version has emerged recently.

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.

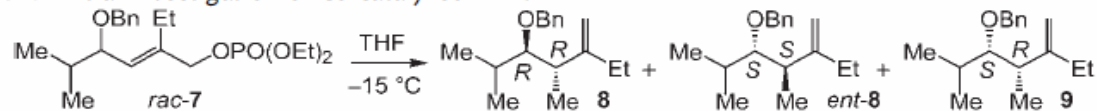


The challenges:

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

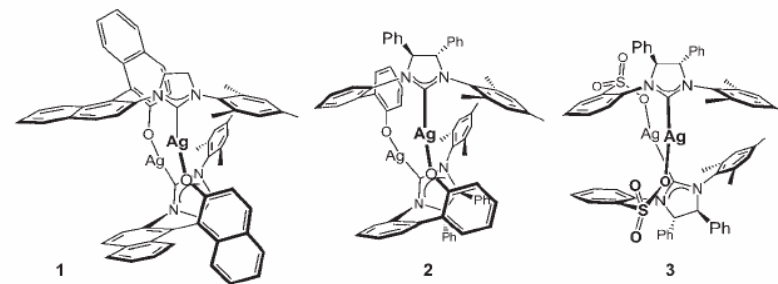
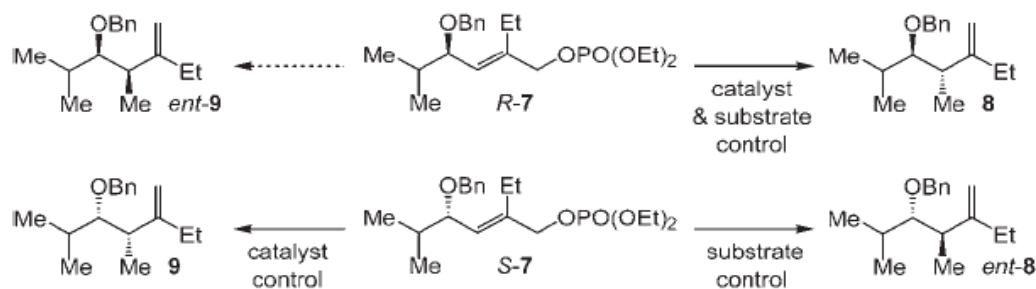
# Left Hand Fragment: Model Study

**Table 1:** Initial investigation of Cu-catalyzed AAA.<sup>[a]</sup>

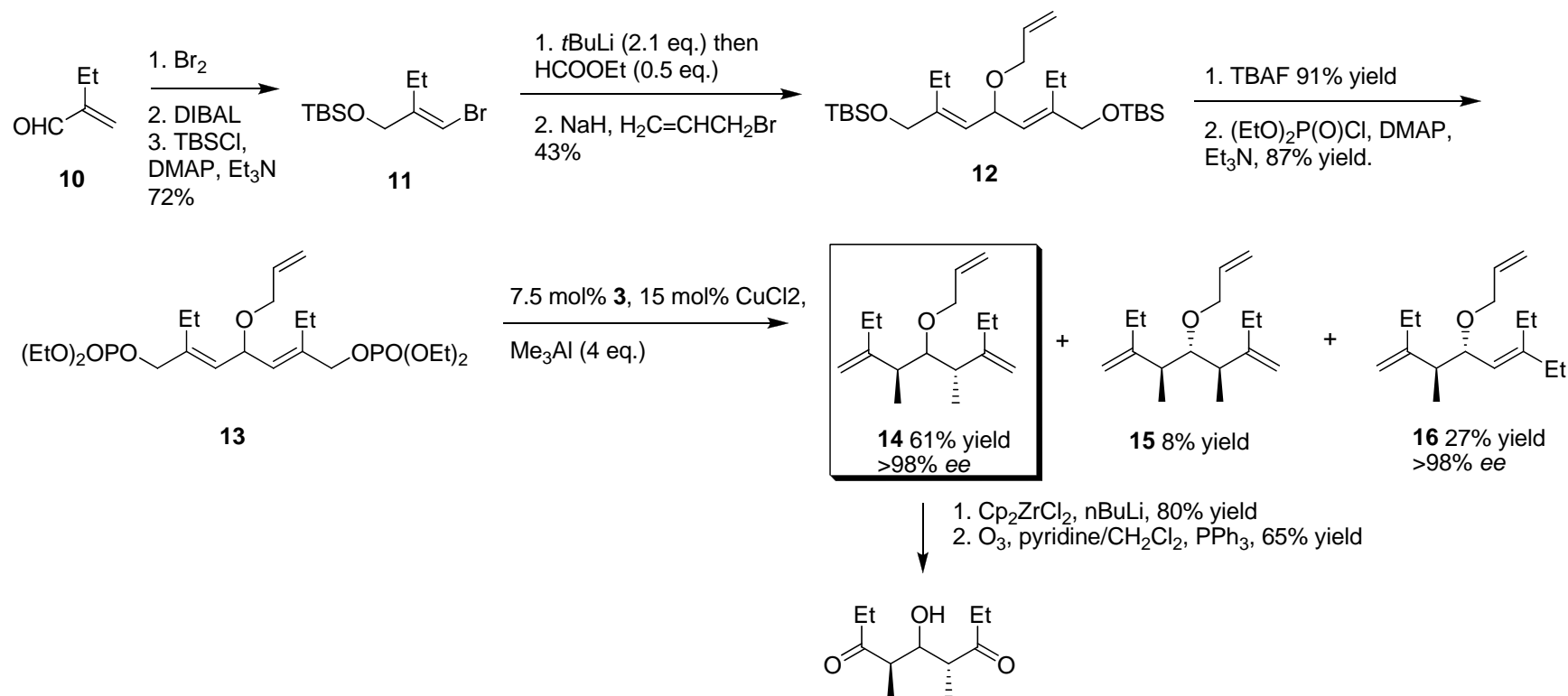


Entry	Alkyl metal	Catalyst (mol%)	Conv. [%] <sup>[b]</sup>	t [h]	<i>S<sub>N</sub>2'</i> : <i>S<sub>N</sub>2</i> <sup>[b]</sup>	8:9 <sup>[b]</sup>	e.r. [%] 8 <sup>[c]</sup>	ee [%] 8 <sup>[c]</sup>
1	Me <sub>2</sub> Zn	CuCN (200)	10	24	> 20:1	9:1	–	–
2	Me <sub>2</sub> Zn	1 (7.5); CuCl <sub>2</sub> ·2H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

[a] Reactions were performed under N<sub>2</sub>. [b] Determined by 400-MHz <sup>1</sup>H NMR analyses of unpurified mixtures. [c] Determined by chiral GLC analysis (see the Supporting Information for details). nd = not determined.

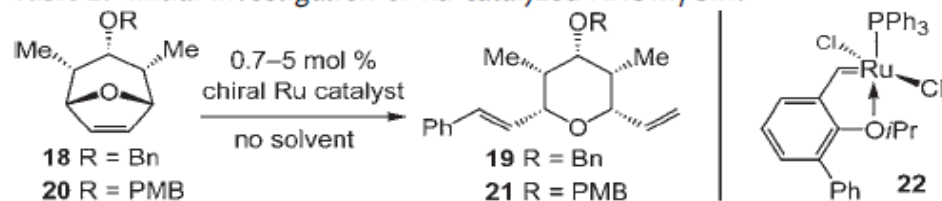


# Left Hand Fragment: Synthesis



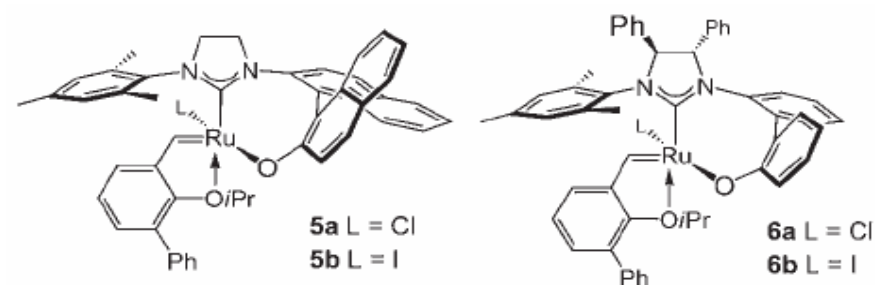
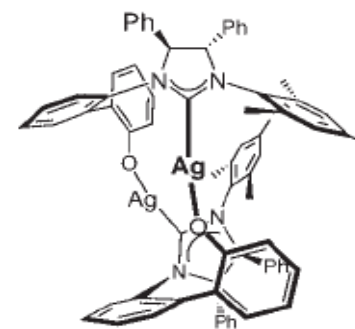
# Right Hand Fragment: AROM/CM

**Table 2:** Initial investigation of Ru-catalyzed AROM/CM.<sup>[a]</sup>

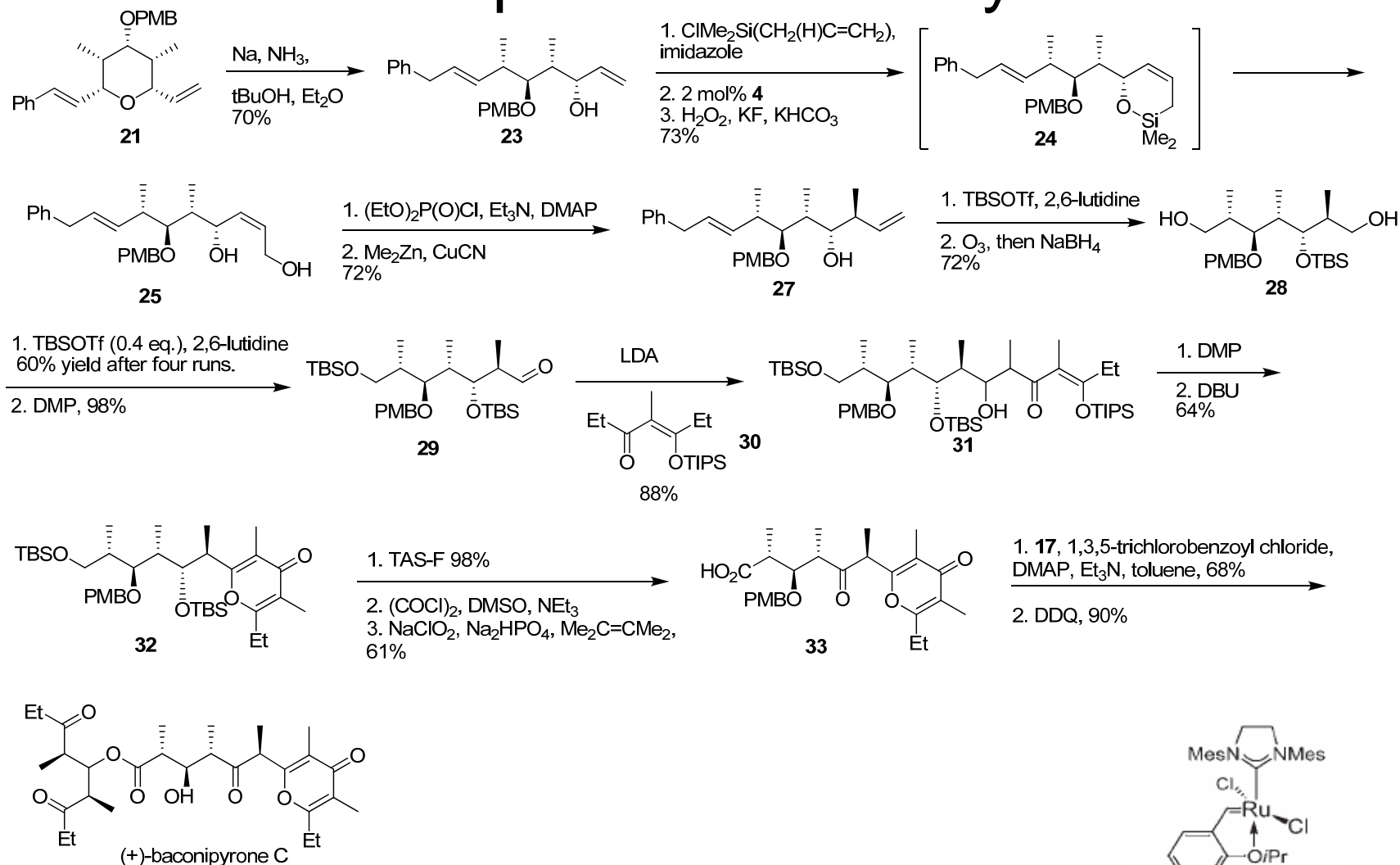


Entry	Substrate	Catalyst (mol %)	Equiv styrene	T [°C]; t [h]	Conv. [%] <sup>[b]</sup> ; Yield [%] <sup>[c]</sup>	ee [%] <sup>[d]</sup>
1	18	5b (5)	4	22; 44	96; 55	80
2	18	6b (5)	4	22; 15	>98; 56	81
3	18	2 + 22 + NaI (2.5)	4	22; 14	>98; 44	81
4	18	2 + 22 + NaI (0.7)	4	22; 14	>98; 46	73
5	18	2 + 22 + NaI (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 N<sub>2</sub>. [b] Conversions were determined by 400-MHz <sup>1</sup>H 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.