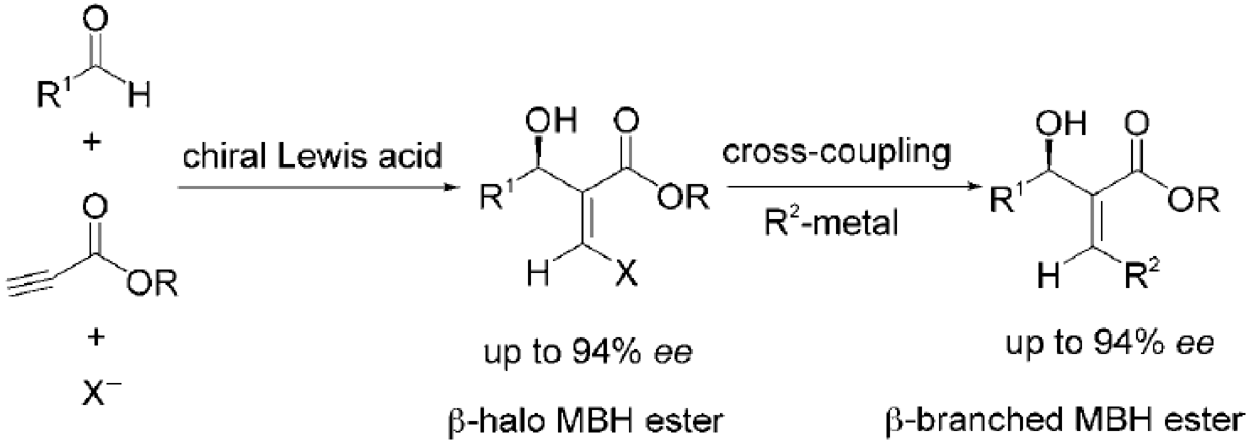
Enantioselective Synthesis of β-Iodo Morita–Baylis–Hillman Esters by a Catalytic Asymmetric Three-Component Coupling Reaction**

*Bidyut Kumar Senapati, Geum-Sook Hwang, Sungil Lee, and Do Hyun Ryu**

Angewandte Chemie Int. Ed. **2009**, early view.



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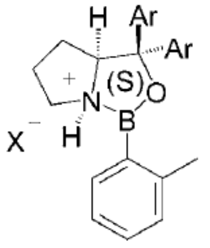
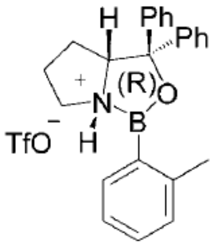


1a: Ar = phenyl, X = TfO
1b: Ar = phenyl, X = Tf_2N
1c: Ar = 3,5-dimethylphenyl(mexyl), X = TfO



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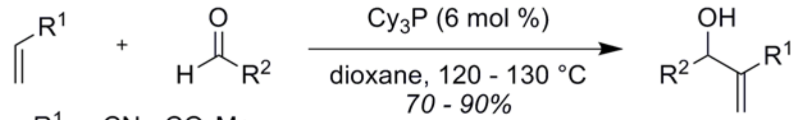
Nolan D. Griggs – 5-22-2009

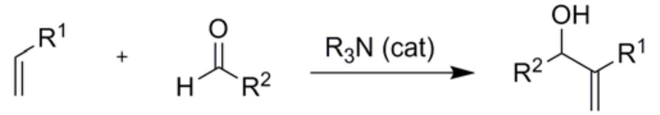
The Morita-Baylis Hillman Reaction - Overview

- First example by Morita and co-workers in 1968:
  Morita, K., Suzuki, Z., Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, 41, 2815.

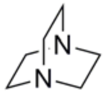


R^1 = -CN, $-CO_2Me$
R^2 = alkyl, aryl

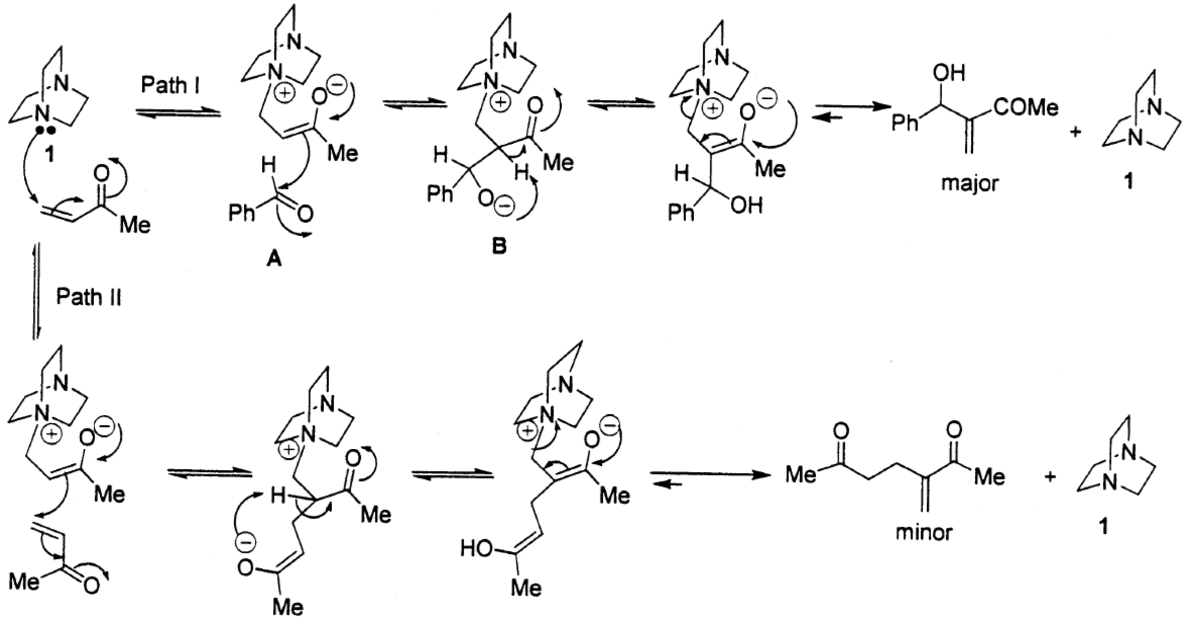
- Later published 1972 by Baylis and Hillman in a German patent:
  Baylis, A.B., Hillman, M.E.D. *Acrylic Compounds.* De 2155113, **1972** (Celanese Corp.).



Use of DABCO first reported:



- Proposed Mechanism:

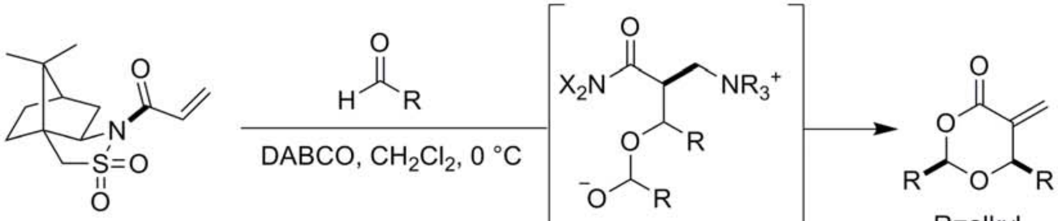


- Reviews:

- *ACIEE* **2007,** *46,* 4614
- *Eur. J. Org. Chem.*, **2007**, 2905
- *Chem. Soc. Rev.,* **2007**, *36,* 1581
- *Chem. Rev.* **2003**, *103*, 811.

Asymmetric Morita-Baylis-Hillman Reaction

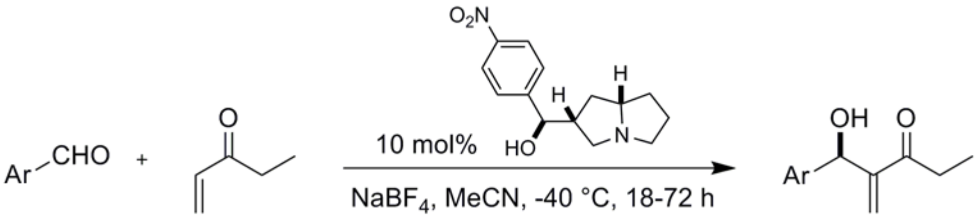
- Auxillary based:



R=alkyl
Yields = 33 - 98%
%ee = >99

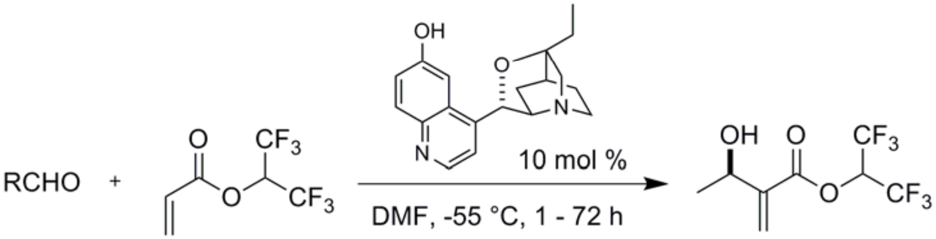
Leahy, J. et. al. *J. am. Chem. Soc.* **1997**, *119*, 4317.

- Organocatalytic methods:



Yields = 31 - 93%
%ee = 39 - 72

Barrett, A. et. al. *Chem. Comm*, **1998**, 2533.



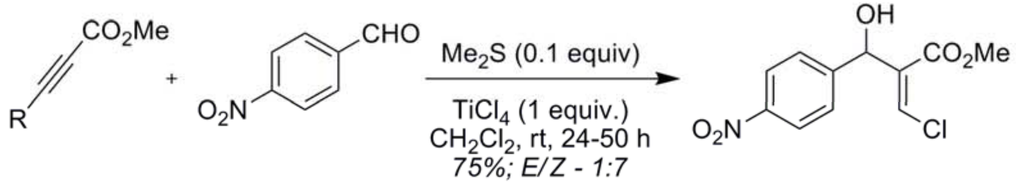
Yields = 31 - 58%
%ee = 91 - 99

Hatakeyama, S. et. al. *J. Am. Chem. Soc.* **1999**, *121*, 10219.

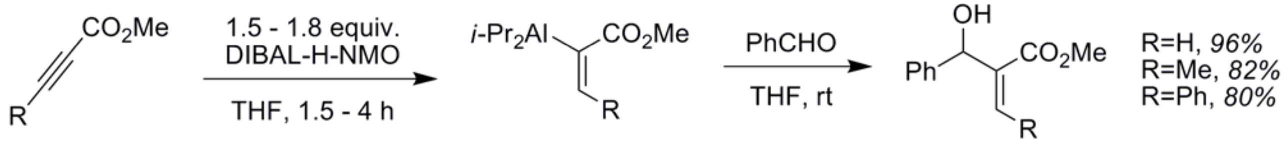
For a review, see: Langer, P. *Angew. Chemie. Int. Ed.*, **2000**, *39*, 3049.

Stereochemical Control of β-branched MBH products

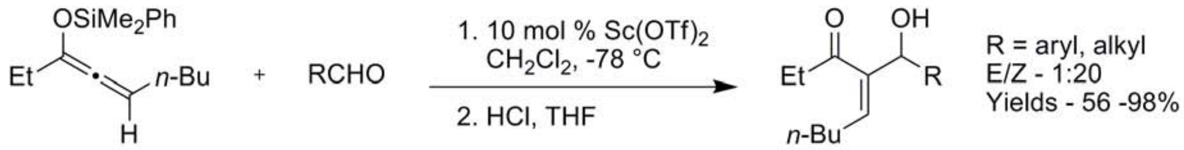
- Kataoka and co-workers - *Angew. Chemie. Int. Ed.* **2000,** *39*, 2358.



- Ramachandran and co-workers - *J. Org. Chem,* **2003**, *68*, 9310.

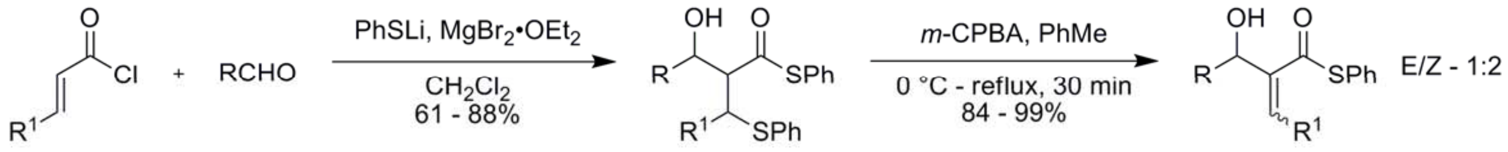


- Scheidt and co-workers - *J. Am. Chem. Soc.* **2006**, *128, 15382.*



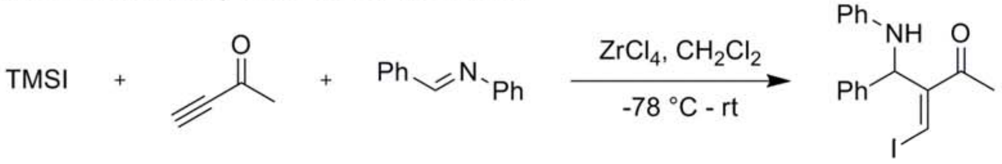
- For an asymmetric version using (Salen)CrSbF$_6$ w/ ee = 61-94%, see: *Angew. Chemie. Int. Ed.,* **2007**, *46,* 7806.

- Coltart and co-workers - *Org. Lett.*, **2008**, *10*, 4819.



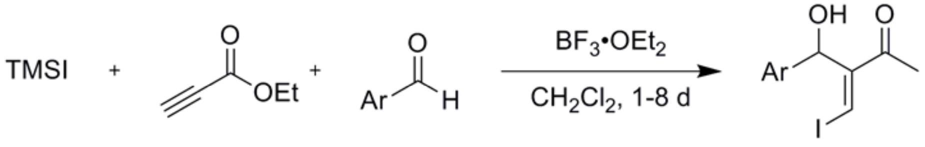
Synthesis of β-halo MBH products

- *E*-stereocontrolled β-halo MBH products:



Exclusively *E*-olefin; yields = 76 - 97%

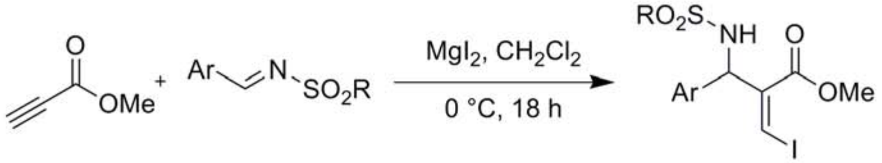
Shi, M. et. al. *Tetrahedron Lett.* **2006**, *47*, 7699.



yields = 60 - 91%, E/Z = >89:11

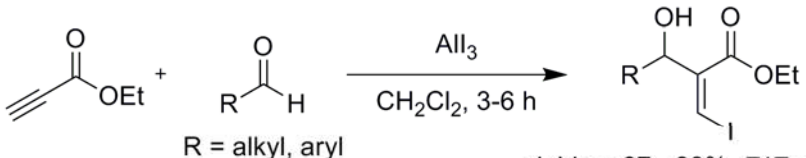
Ryu, D.H. et al. *Org. Lett.* **2007**, *9*, 5087

- *Z*-stereocontrolled β-halo MBH products: Review - *Recent Res. Dev. Org. Bioorg. Chem.* **2001**, 49.



yields = 68 - 84%; *Z*/*E* = >17:1

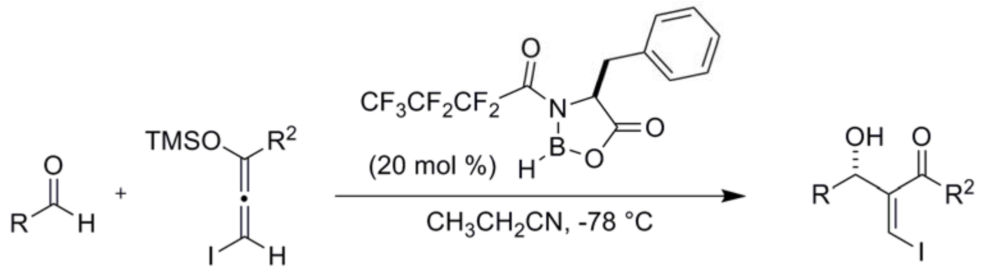
Li, G., Timmons, C. et. al. *Tetrahedron*, **2006**, 7151.



yields = 67 - 90%, *Z*/*E* = >82:18

Ryu, D.H. et al. *Synlett.* **2007**, *59.*

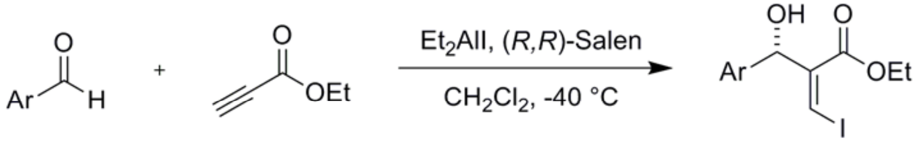
Asymmetric Synthesis of β-iodo MBH products



R, R^2 = alkyl, aryl

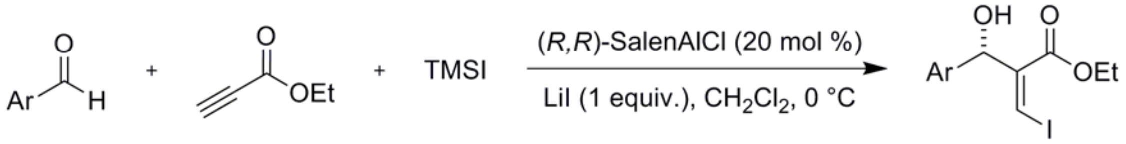
(60 - 75%, 61 - 98 %*ee*, *E*/*Z* = 1:1.8 - <1:20)

Li, G. et. al. *Org. Lett* **2001**, *3*, 823.



(55 - 80%, 49 - 76 %*ee*, *E*/*Z* = <1:20)

Li, G., Timmons, C. et al. *Eur. J. Org. Chem.* **2004**, 3330.

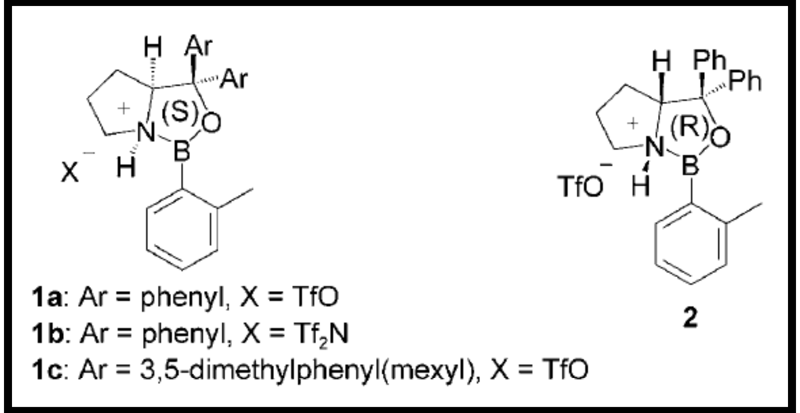


(40 - 82%, 50 - 62 %*ee*, *E*/*Z* = <1:20)

Li, G., *Tetrahedron: Asymm.* **2005**, 1757.

Title Paper:
Catalytic Asymmetric Synthesis of β-Iodo MBH Products

- Initial Screening:



1a: Ar = phenyl, X = TfO
1b: Ar = phenyl, X = Tf_2N
1c: Ar = 3,5-dimethylphenyl(mexyl), X = TfO

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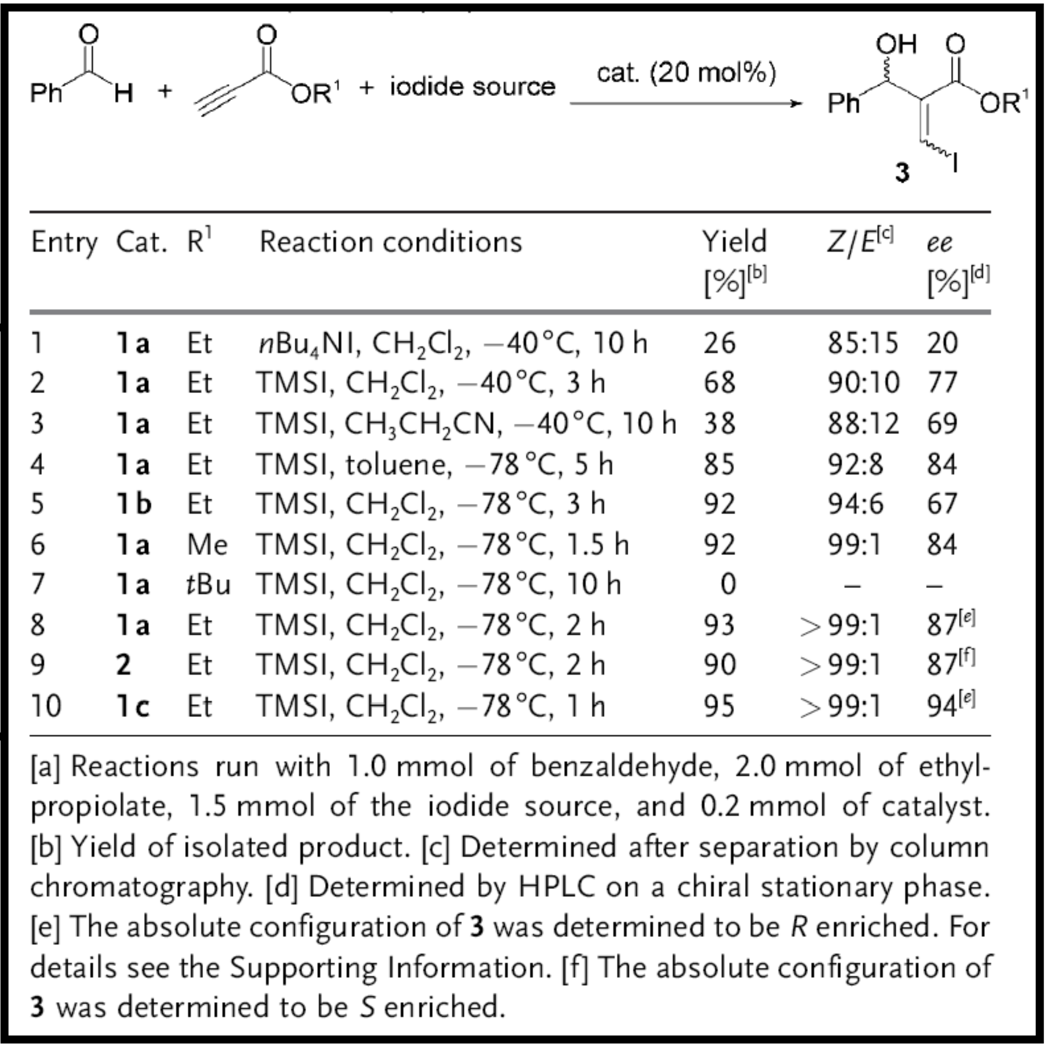
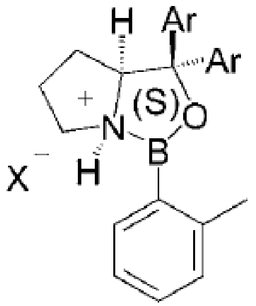


Entry	Cat.	R^1	Reaction conditions	Yield [%][b]	Z/E[c]	ee [%][d]
1	**1a**	Et	nBu$_4$NI, CH_2Cl_2, −40°C, 10 h	26	85:15	20
2	**1a**	Et	TMSI, CH_2Cl_2, −40°C, 3 h	68	90:10	77
3	**1a**	Et	TMSI, CH_3CH_2CN, −40°C, 10 h	38	88:12	69
4	**1a**	Et	TMSI, toluene, −78°C, 5 h	85	92:8	84
5	**1b**	Et	TMSI, CH_2Cl_2, −78°C, 3 h	92	94:6	67
6	**1a**	Me	TMSI, CH_2Cl_2, −78°C, 1.5 h	92	99:1	84
7	**1a**	*t*Bu	TMSI, CH_2Cl_2, −78°C, 10 h	0	–	–
8	**1a**	Et	TMSI, CH_2Cl_2, −78°C, 2 h	93	> 99:1	87[e]
9	**2**	Et	TMSI, CH_2Cl_2, −78°C, 2 h	90	> 99:1	87[f]
10	**1c**	Et	TMSI, CH_2Cl_2, −78°C, 1 h	95	> 99:1	94[e]

[a] Reactions run with 1.0 mmol of benzaldehyde, 2.0 mmol of ethylpropiolate, 1.5 mmol of the iodide source, and 0.2 mmol of catalyst. [b] Yield of isolated product. [c] Determined after separation by column chromatography. [d] Determined by HPLC on a chiral stationary phase. [e] The absolute configuration of **3** was determined to be *R* enriched. For details see the Supporting Information. [f] The absolute configuration of **3** was determined to be *S* enriched.

Title Paper:
Catalytic Asymmetric Synthesis of β-Iodo MBH Products

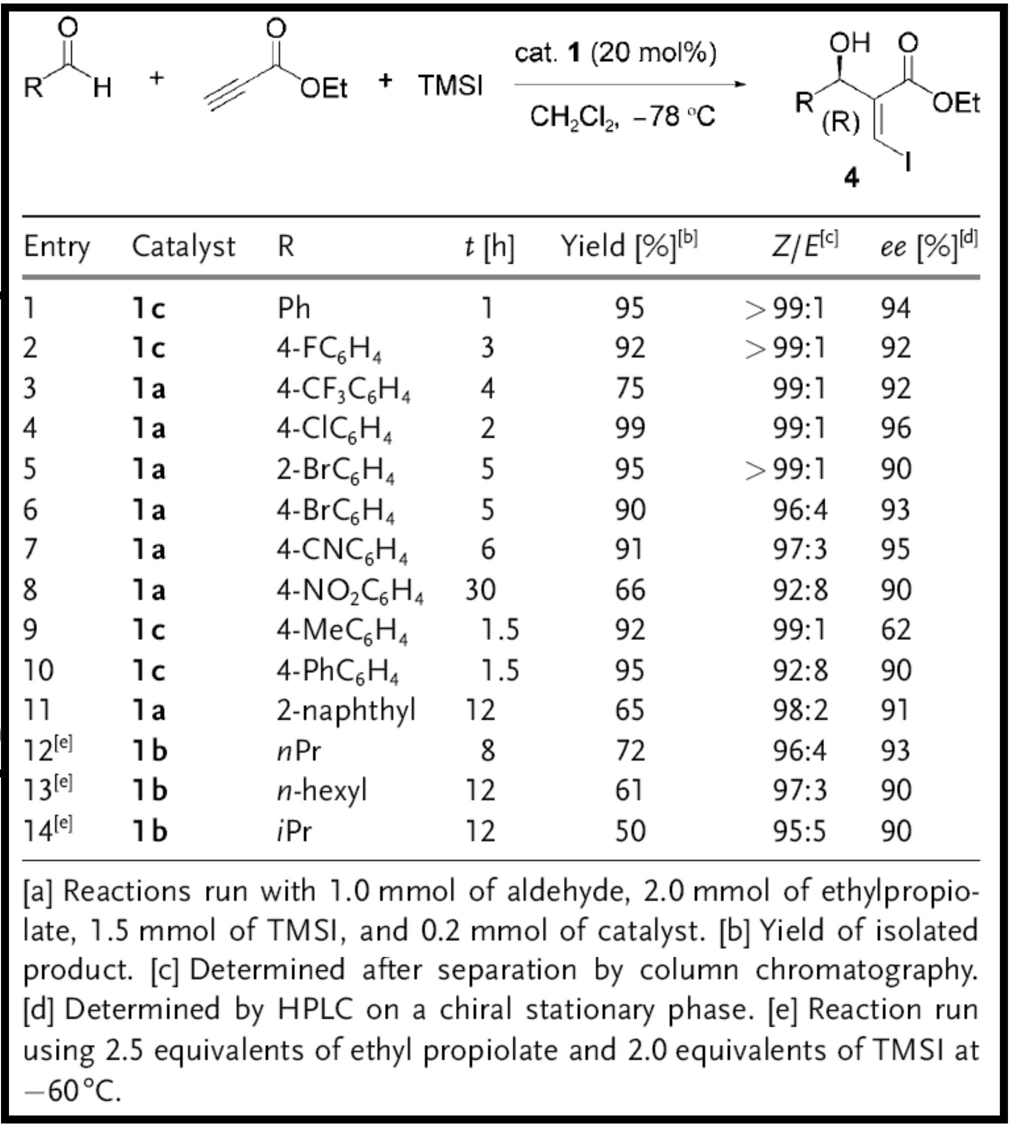
- Scope and Limitations:



1a: Ar = phenyl, X = TfO

1b: Ar = phenyl, X = Tf_2N

1c: Ar = 3,5-dimethylphenyl(mexyl), X = TfO

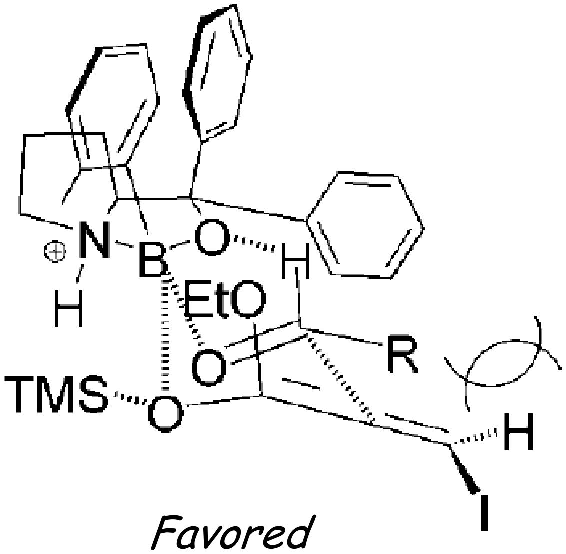


Entry	Catalyst	R	*t* [h]	Yield [%][b]	*Z*/*E*[c]	*ee* [%][d]
1	**1c**	Ph	1	95	>99:1	94
2	**1c**	4-FC_6H_4	3	92	>99:1	92
3	**1a**	4-$CF_3C_6H_4$	4	75	99:1	92
4	**1a**	4-ClC_6H_4	2	99	99:1	96
5	**1a**	2-BrC_6H_4	5	95	>99:1	90
6	**1a**	4-BrC_6H_4	5	90	96:4	93
7	**1a**	4-CNC_6H_4	6	91	97:3	95
8	**1a**	4-$NO_2C_6H_4$	30	66	92:8	90
9	**1c**	4-MeC_6H_4	1.5	92	99:1	62
10	**1c**	4-PhC_6H_4	1.5	95	92:8	90
11	**1a**	2-naphthyl	12	65	98:2	91
12[e]	**1b**	*n*Pr	8	72	96:4	93
13[e]	**1b**	*n*-hexyl	12	61	97:3	90
14[e]	**1b**	*i*Pr	12	50	95:5	90

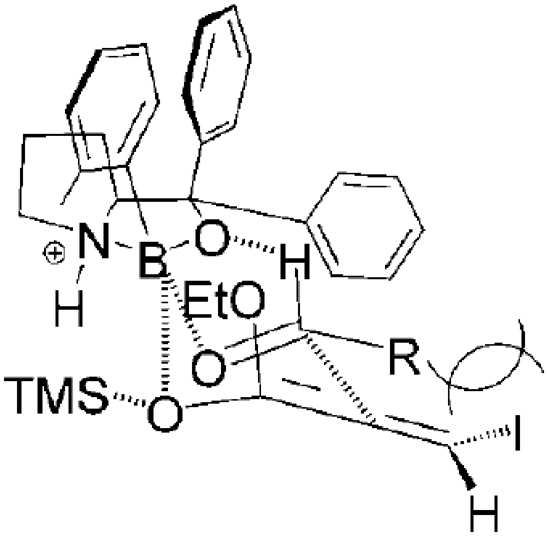
[a] Reactions run with 1.0 mmol of aldehyde, 2.0 mmol of ethylpropiolate, 1.5 mmol of TMSI, and 0.2 mmol of catalyst. [b] Yield of isolated product. [c] Determined after separation by column chromatography. [d] Determined by HPLC on a chiral stationary phase. [e] Reaction run using 2.5 equivalents of ethyl propiolate and 2.0 equivalents of TMSI at −60 °C.

Title Paper:
Catalytic Asymmetric Synthesis of β-Iodo MBH Products

- Proposed Transition-state model:



Favored

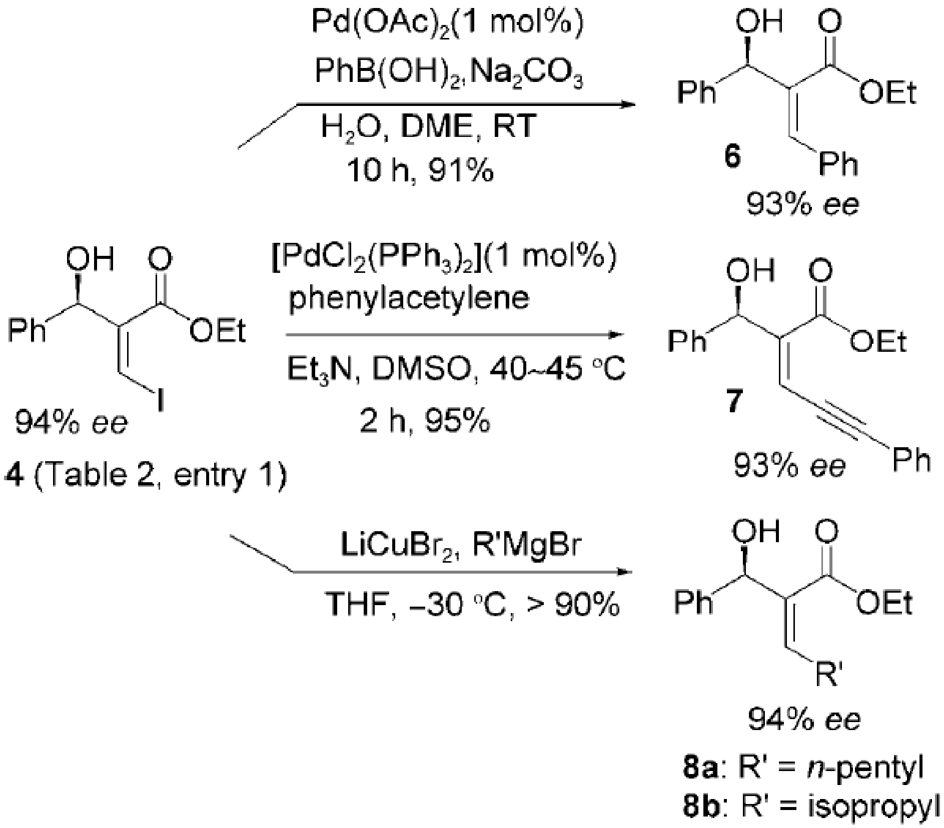


For similar oxazaborolidinium catalyst complexes involving aldehydes, see:
Ryu, D.H., Corey, E.J. *J. Am. Chem. Soc.* **2003**, *125,* 6388.
Ryu, D.H., Corey, E.J. *J. Am. Chem. Soc.* **2004**, *126,* 8106.

For discussion of pentacoordinated boron species, see:
Maruoka, J. et al. *J. Am. Chem. Soc.* **1998**, *120,* 5327.

Title Paper:
Catalytic Asymmetric Synthesis of β-Iodo MBH Products

- Further Application of MBH adducts:



Bumagin, N.A., et. al. *Tetrahedron* **1997**, *53,* 14437.

Lu, Z. et. al. *J. Org. Chem.* **2006**, *71,* 2655.

Ayed, T.B. et. al. *Tetrahedron.* **2000**, *56,* 805.

Conclusions

- Ryu, D.H. and co-workers have developed a catalytic, highly enantioselective three-component coupling between an aldehyde, ethyl propiolate, and TMSI to give optically active (*Z*)-β-iodo Morita-Baylis-Hillman esters.

- Both enantiomers are accessible using the appropriate, readily available oxazaborolidinium catalyst, and the absolute configuration matches that predicted by the transition state model.

- Further functionalization of the product vinyl iodides led to highly functionalized, optically active *Z*-olefin-containing products.