

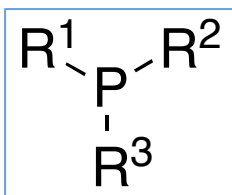
Phosphine-catalyzed enantioselective γ -addition of 3-substituted oxindoles to 2,3-butadienoates and 2-butynoates: use of prochiral nucleophiles

Tianli Wang, Weijun Yao, Fangrui Zhong, Guo Hao Pang, and Yixin Lu*

Angew. Chem. Int. Ed., **2014**, 53, 2964–2968.

Eakkaphon Rattanangkool
Wipf Group-Current Literature

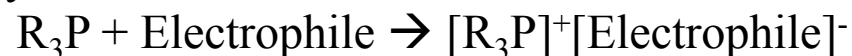
Phosphines



Weaker bases, but stronger nucleophiles than nitrogen analogs

React with saturated and unsaturated C, O, S, X(VII A), and N

Practically all useful transformations involve



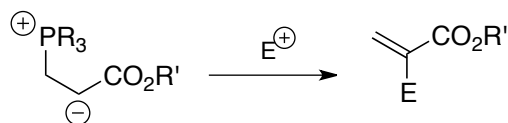
Can be a leaving group (catalysis)

Basicity and Structure			
	pK_a	Bond angles	Bond length
Me ₃ P	8.67	99°	1.84 Å
Me ₃ N	9.76	108°	1.47 Å

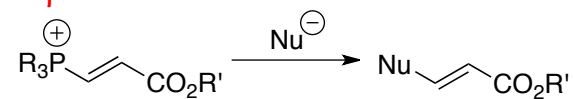
Organophosphorus Reagents in Organic Synthesis, Ed. By J.I.G. Cadogan, Academic Press, © 1979

Phosphine Catalyzed Reactions

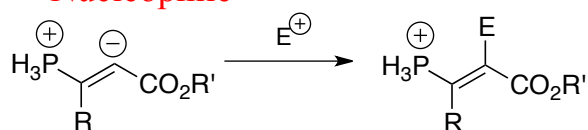
Morita-Baylis-Hillman



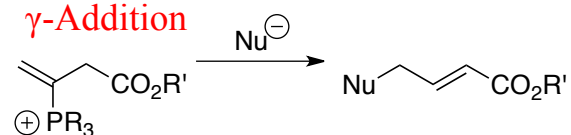
β -Addition



Nucleophile



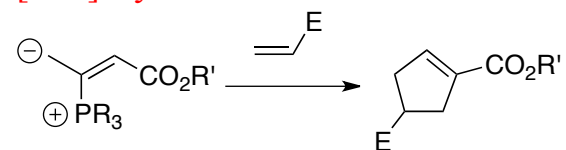
γ -Addition



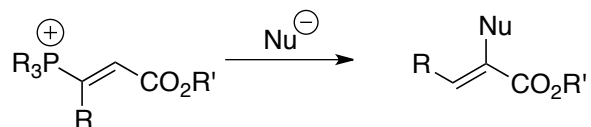
Isomerization



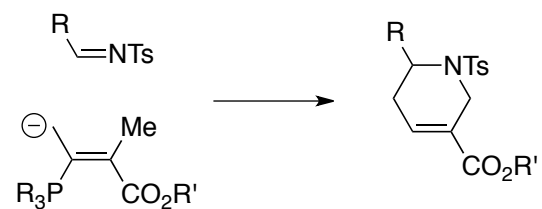
[3+2] Cycloaddition



α -Addition

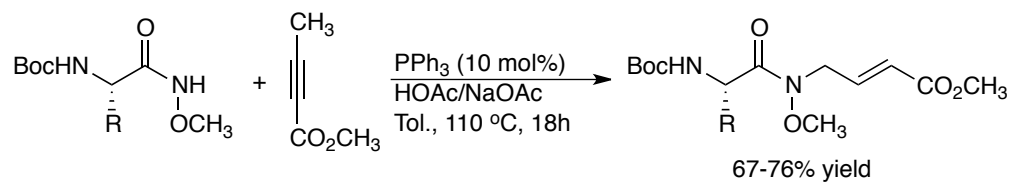


[4+2] Annulation



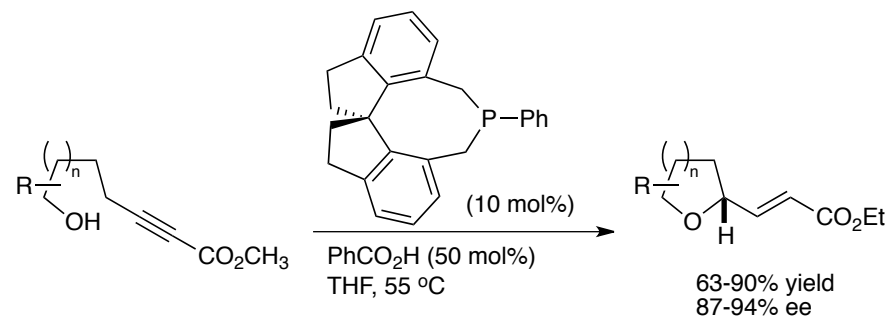
Phosphine Catalyzed Reactions

γ -Addition reaction of nitrogen



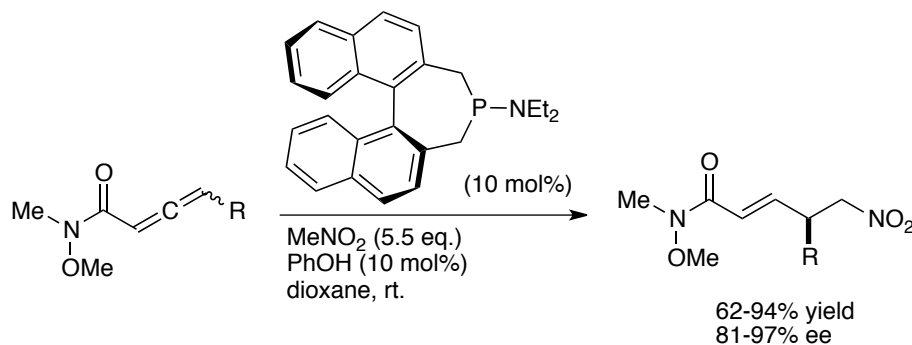
J. Org. Chem., **1997**, 62, 5670-5671.

γ -Addition reaction of oxygen



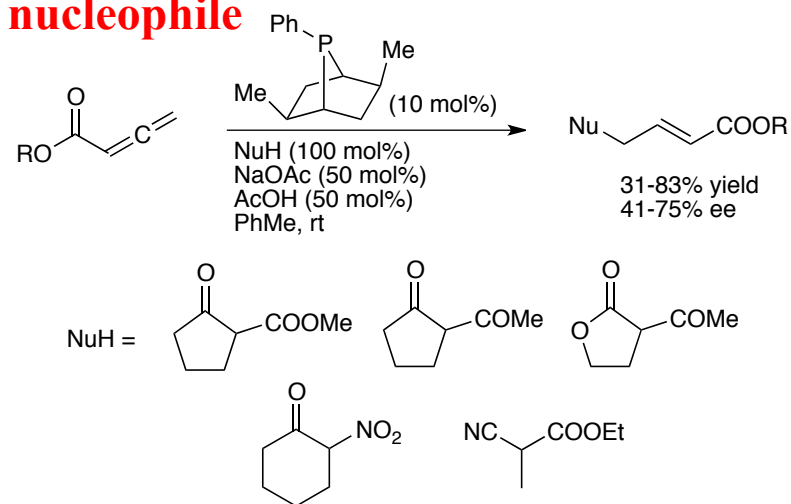
Angew. Chem. Int. Ed., **2009**, 48, 2225–2227.

γ -Addition reaction of carbon



J. Am. Chem. Soc., **2009**, 131, 14231–14233.

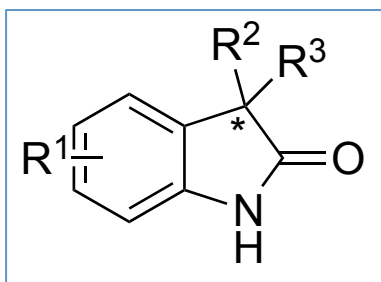
γ -Addition reaction via prochiral nucleophile



J. Org. Chem., **1998**, 63, 5631-5635.

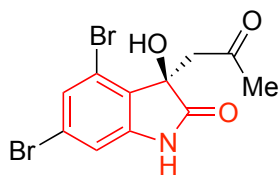
05/10/2013

Oxindoles

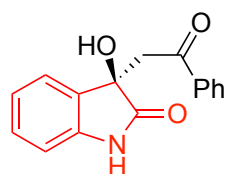


Found in natural products

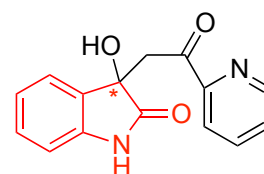
Prominent substructure in bioactive molecules



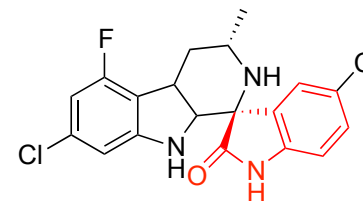
Antinociceptive
(R)-convolutamydin A



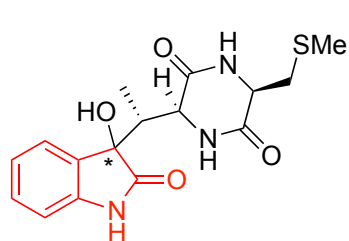
Anticonvulsant agent



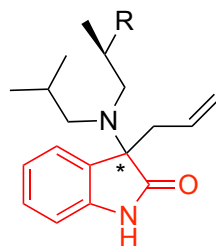
Antidegenerative
disease agent



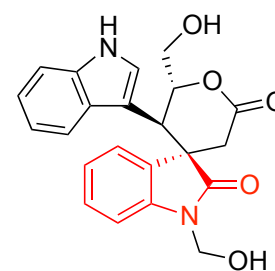
Antimalarial
NITD609



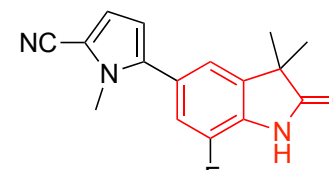
—OH Maremycin A
---OH Maremycin B



HIV Protease inhibitor



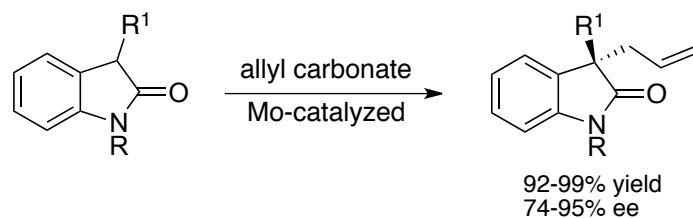
AChE inhibitor
Trigolutes A



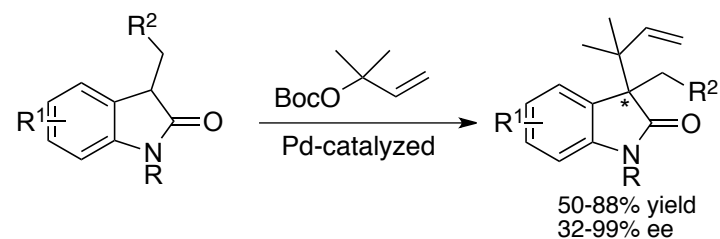
Potent on progesterone
receptor antagonist
WAY-255348

Org. Lett., **2012**, *14*, 4018-4021.; *Org. Biomol. Chem.*, **2014**, *12*, 1885-1891.;
Science **2010**, *329*, 1175-1180.; *J. Med. Chem.*, **2008**, *51*, 1861-1873.

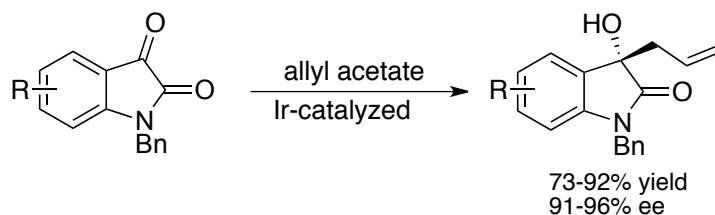
Synthesis of 3,3'-disubstituted oxindole



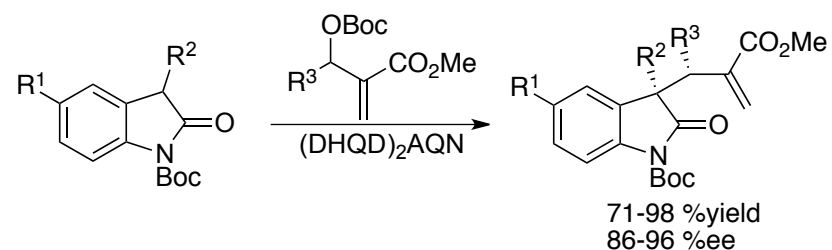
J. Am. Chem. Soc., **2006**, *128*, 4590.



J. Am. Chem. Soc., **2011**, *133*, 7328.

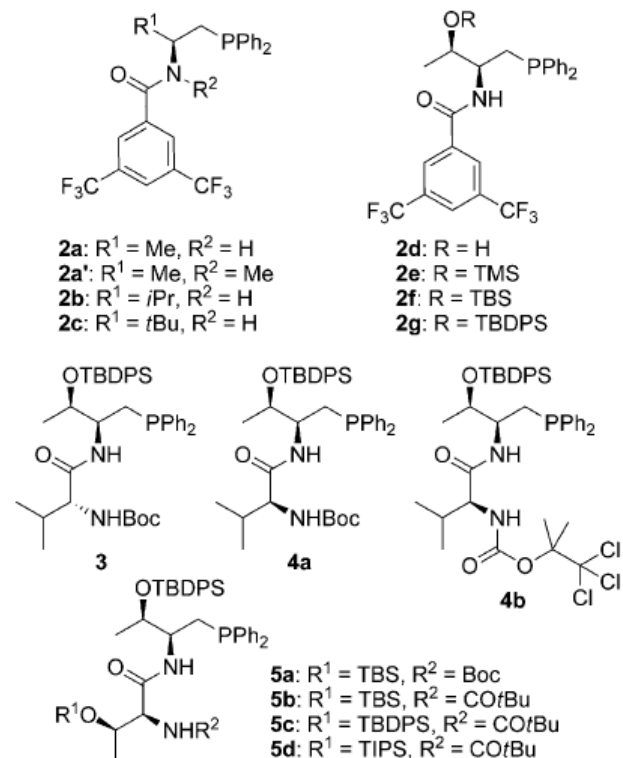
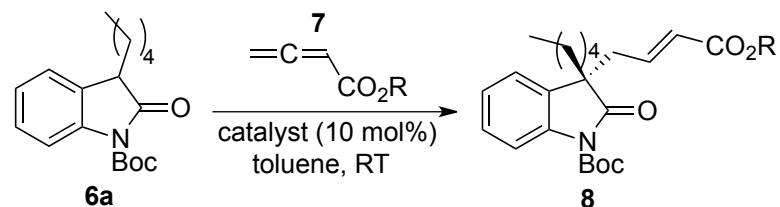
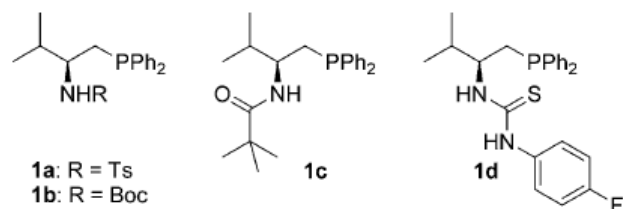
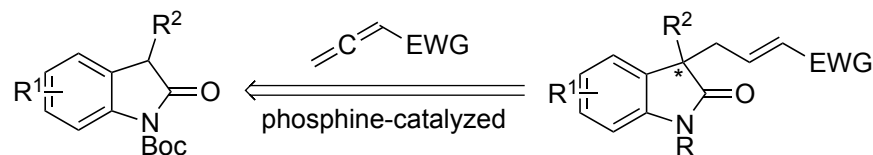


Angew. Chem. Int. Ed., **2009**, *48*, 6313



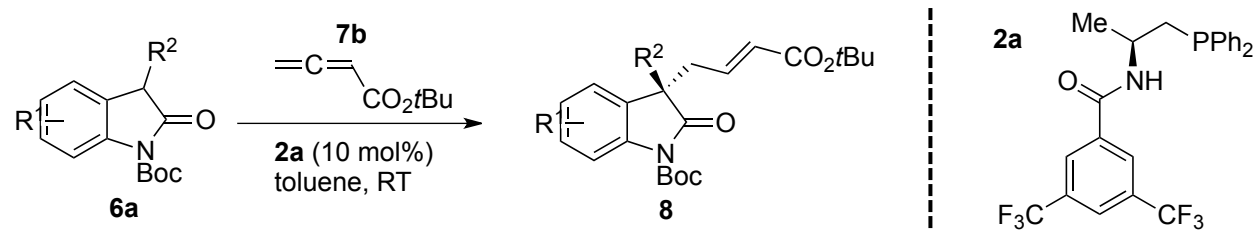
Chem. Commun., **2009**, 3955.

Aim and Optimization



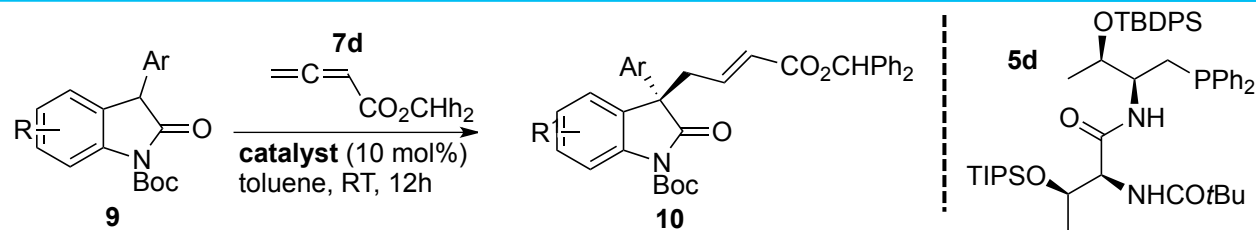
Entry	Catalyst	<i>t</i> [h]	R	8	Yield ^[b] [%]	<i>ee</i> ^[c] [%]
1	1 a	15	CHPh ₂	8 a-4	67	20
2	1 b	15	CHPh ₂	8 a-4	78	27
3	1 c	15	CHPh ₂	8 a-4	62	21
4	1 d	18	CHPh ₂	8 a-4	82	53
5	2 a	15	CHPh ₂	8 a-4	93	86
6	2 b	15	CHPh ₂	8 a-4	90	79
7	2 c	24	CHPh ₂	8 a-4	79	60
8	2 d	24	CHPh ₂	8 a-4	79	60
9	2 e	15	CHPh ₂	8 a-4	90	80
10	2 f	15	CHPh ₂	8 a-4	85	79
11	2 g	15	CHPh ₂	8 a-4	83	78
12	3	24	CHPh ₂	8 a-4	90	5
13	4 a	24	CHPh ₂	8 a-4	86	11
14	2 a	15	Et	8 a-1	96	90
15	2 a	15	<i>t</i> Bu	8 a-2	95	94
16	2 a	15	Bn	8 a-3	94	75

Asymmetric γ -addition of 3-alkyl substituted oxindoles



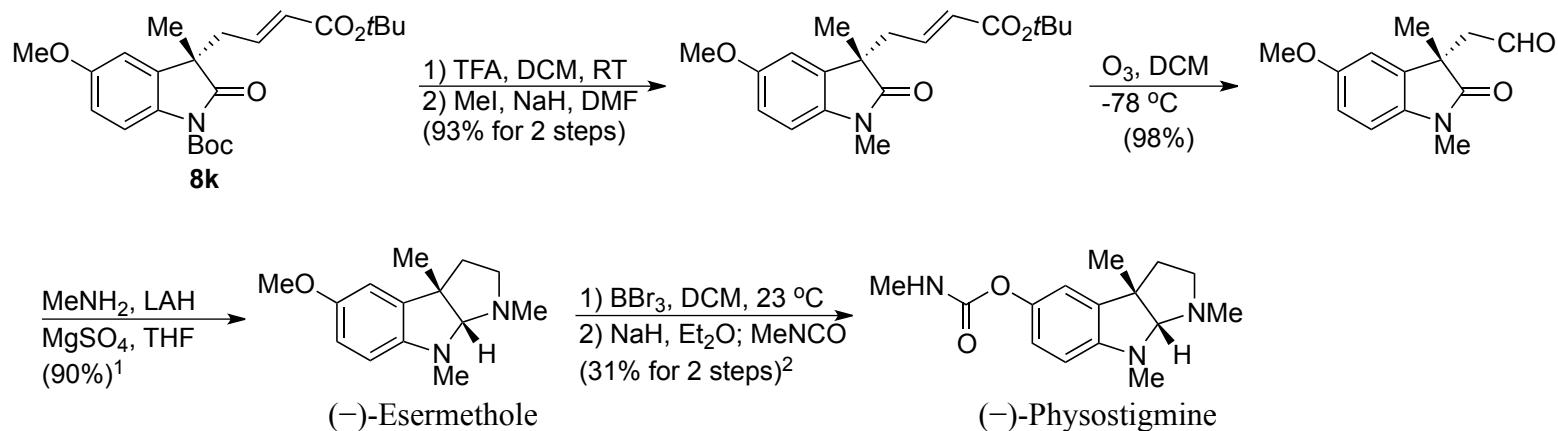
Entry	R ¹	R ²	8	Yield ^[b] [%]	ee ^[c] [%]
1	H	<i>n</i> C ₅ H ₁₁	8a	95	94
2	H	Me	8b	96	88
3	H	Et	8c	96	92
4	H	<i>n</i> Pr	8d	95	89
5	H	<i>i</i> Pr	8e	98	94
6	H	<i>n</i> C ₄ H ₉	8f	95	93
7	H	<i>n</i> C ₆ H ₁₃	8g	98	90
8	H	CH(CH ₂) ₄	8h	92	90
9	H	CH(CH ₂) ₅	8i	97	93
10	H	CH(CH ₂) ₆	8j	91	92
11	5-MeO	Me	8k	98	89
12	5-Br	<i>i</i> Pr	8l	98	85
13	H	CH ₂ Ph	8m	97	81

Asymmetric γ -addition of 3-aryl substituted oxindoles

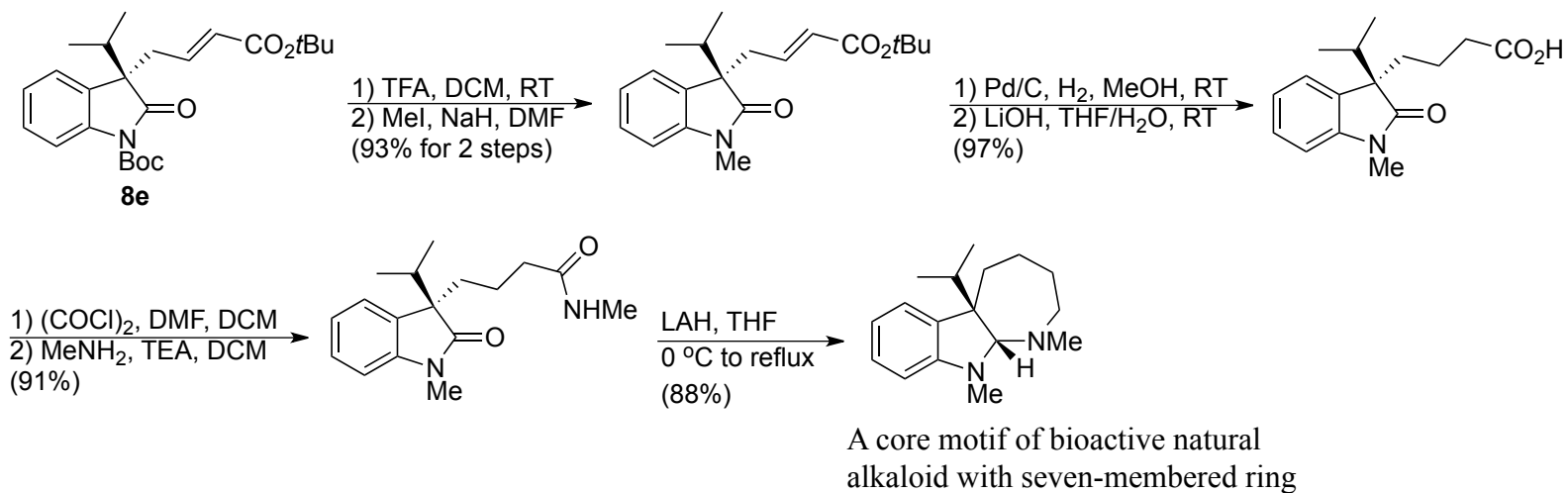


Entry	Ar	R	Cat.	10	Yield ^[b] [%]	ee ^[c] [%]
1	C ₆ H ₅	H	4 a	10a	89	80
2	C ₆ H ₅	H	4 b	10a	87	66
3	C ₆ H ₅	H	5 a	10a	94	83
4	C ₆ H ₅	H	5 b	10a	90	89
5	C ₆ H ₅	H	5 c	10a	89	88
6	C ₆ H ₅	H	5 d	10a	95	91
7	3-Me-C ₆ H ₄	H	5 d	10b	94	86
8	4-Me-C ₆ H ₄	H	5 d	10c	96	90
9	4- <i>t</i> Bu-C ₆ H ₄	H	5 d	10d	93	88
10	4-Ph-C ₆ H ₄	H	5 d	10e	91	90
11	4-MeO-C ₆ H ₄	H	5 d	10f	92	90
12	4-F-C ₆ H ₄	H	5 d	10g	96	88
13	4-Cl-C ₆ H ₄	H	5 d	10h	86	89
14	3,5-Me-C ₆ H ₃	H	5 d	10i	96	90
15	C ₆ H ₅	5-MeO	5 d	10j	95	92
16	C ₆ H ₅	5-Me	5 d	10k	96	90
17	C ₆ H ₅	5-F	5 d	10l	90	86
18	C ₆ H ₅	5,7-Me	5 d	10m	94	82

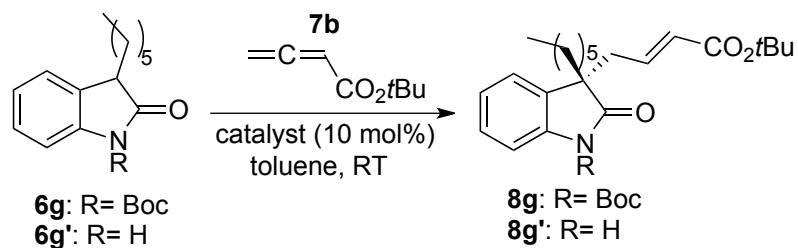
A formal total synthesis of natural products



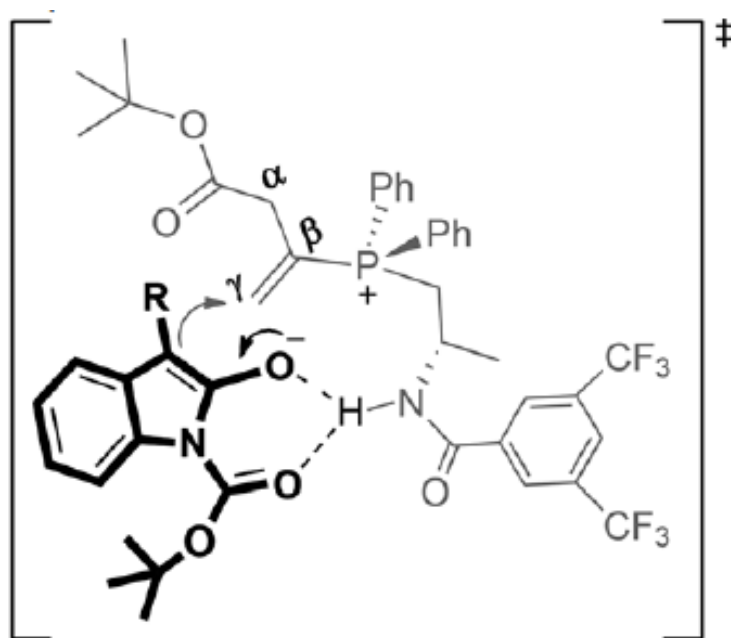
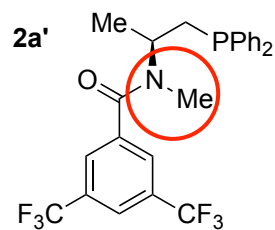
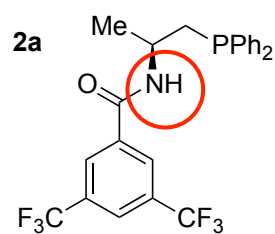
¹*J. Am. Chem. Soc.*, **2004**, *126*, 14043-14053. ²*J. Am. Chem. Soc.*, **1998**, *120*, 6500-6503.



Proposed transition state model



Entry	6	Catalyst	<i>t</i> [h]	8	Yield ^[b] [%]	<i>ee</i> ^[c] [%]
1	6g	2a	15	8g	98	90
2	6g	2a'	36	8g	77	44
3	6g'	2a	36	8g'	81	53



Conclusions

- 3,3'-Disubstituted oxindole compounds were prepared enantioselectively from 3-substituted oxindoles and allenolates using a phosphine-catalyzed asymmetric γ -addition in high yields and excellent enantioselectivities.
- Its synthetic utility was amply demonstrated by the formal total synthesis of natural products and the preparation of molecules of biological significance.

감사합니다 Natick

Grazie

Danke

Ευχαριστίες

Dalu

Thank You

Köszönöm

Tack

Спасибо

Dank

Gracias

谢谢

Merci

Seé

ありがとう

ขอบคุณครับ

Obrigado