Dearomative Indole (3+2) Cycloaddition Reactions

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Date: 2014/05/20

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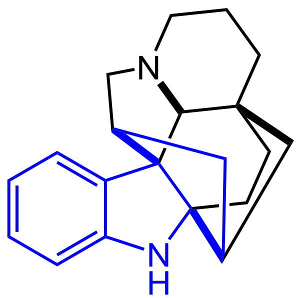
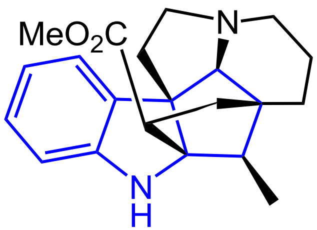
Wu, J. *et al.*
J. Am. Chem. Soc. **2014**, *136*, 6288.

Contents

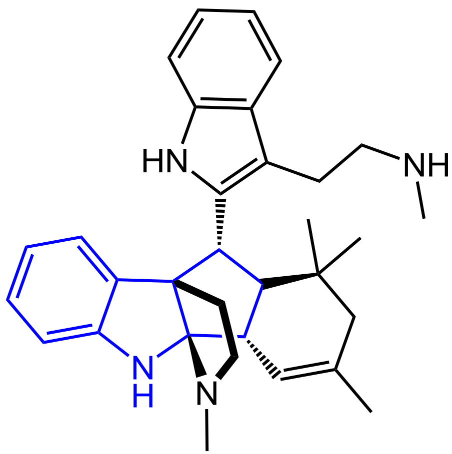
Introduction



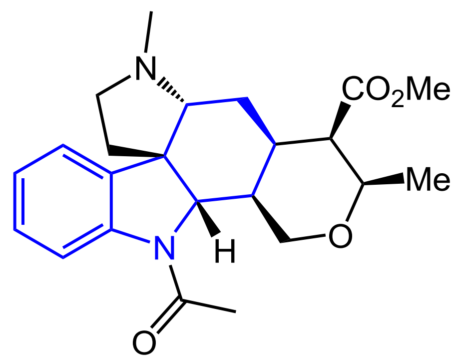
Kopsane



Vindolinine

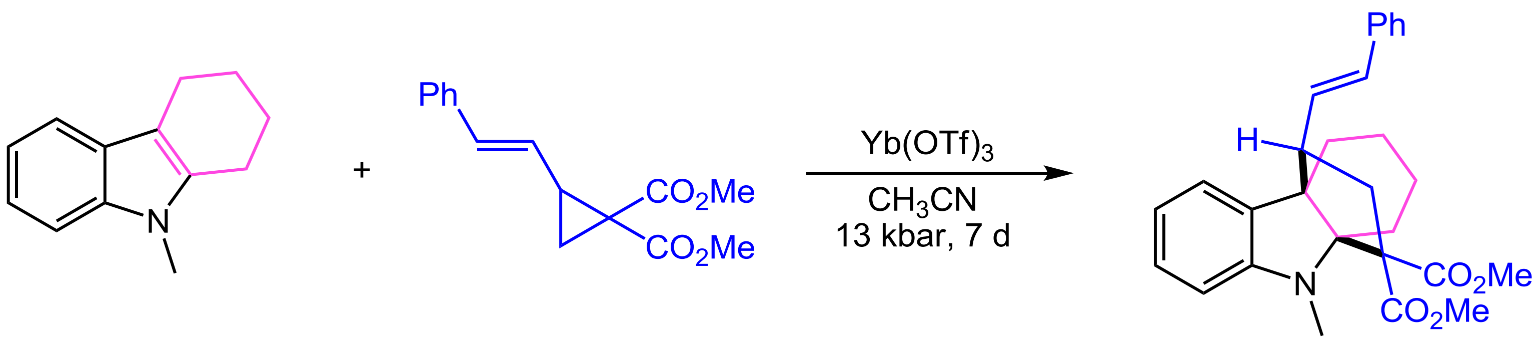


Borreverine

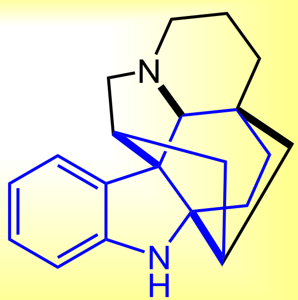


Malagashanine

(3+2) Cycloaddition of Indole with 1,1-Cyclopropane Diesters



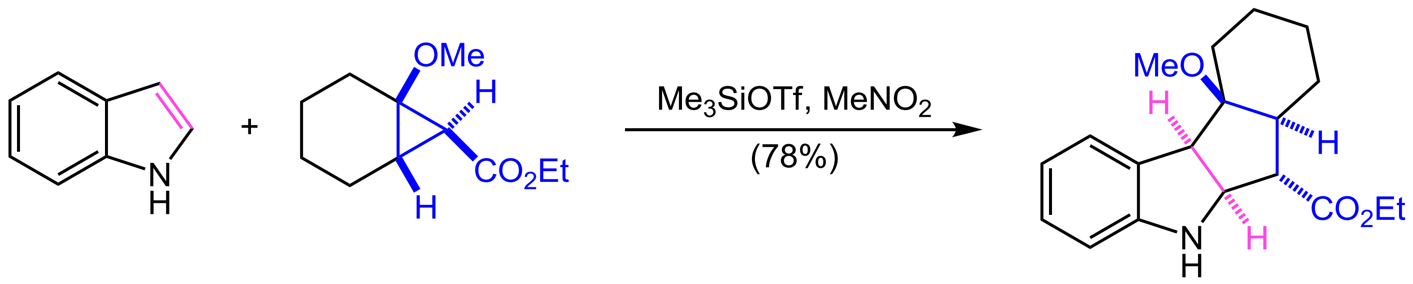
49% yield, 3:1 dr

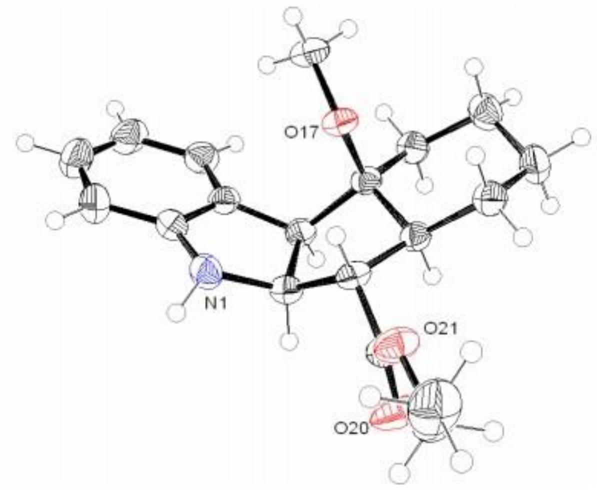


Kopsane

Kerr, M. A. *et al*. *J. Org. Chem.* **2001**, *66*, 4704.

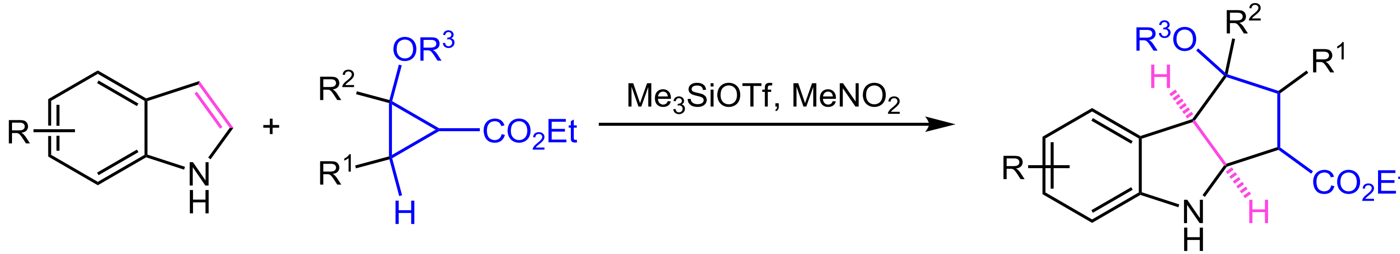
(3+2) Cycloaddition of Indole with 2-Alkoxycyclopropanoate Esters

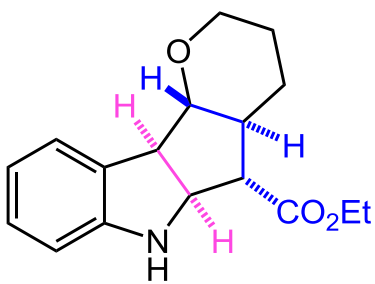




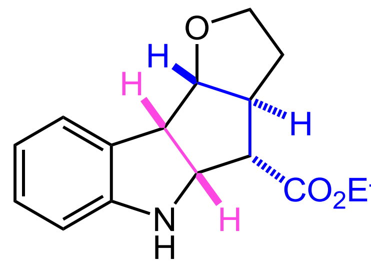
Pagenkopf, B. L. *et al*. *J. Am. Chem. Soc.* **2007**, *129*, 9631.

Substrate Scope

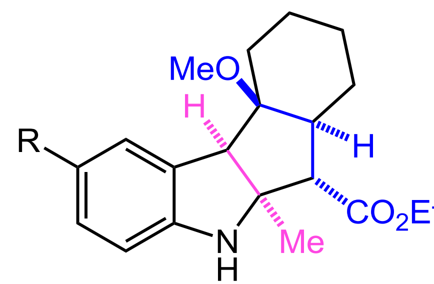




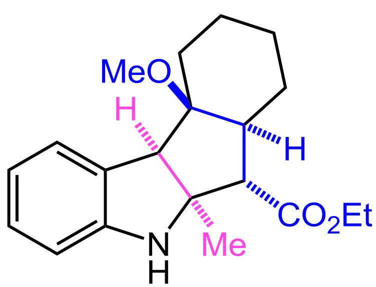
88% yield, 1:1 dr



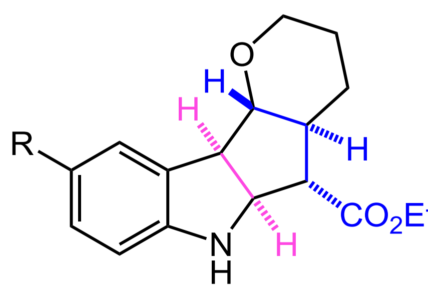
58% yield, 1.3:1 dr



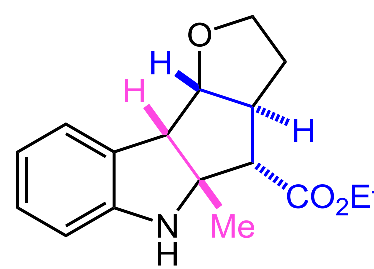
R = Me, 77% yield
R = OMe, 72% yield
R = I, 54% yield



68% yield, 1:1 dr

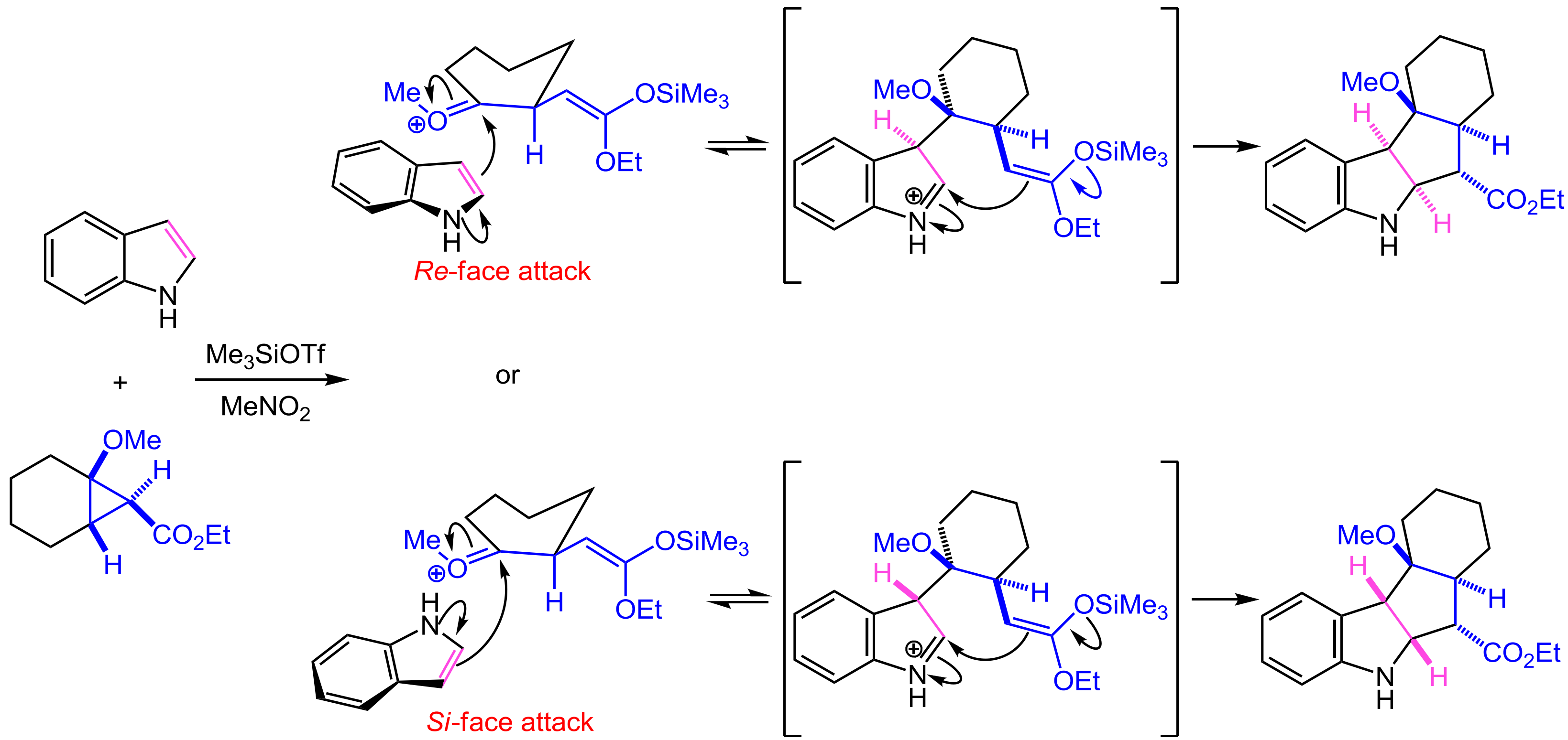


R = OMe, 90% yield, 1:1 dr
R = I, 61% yield

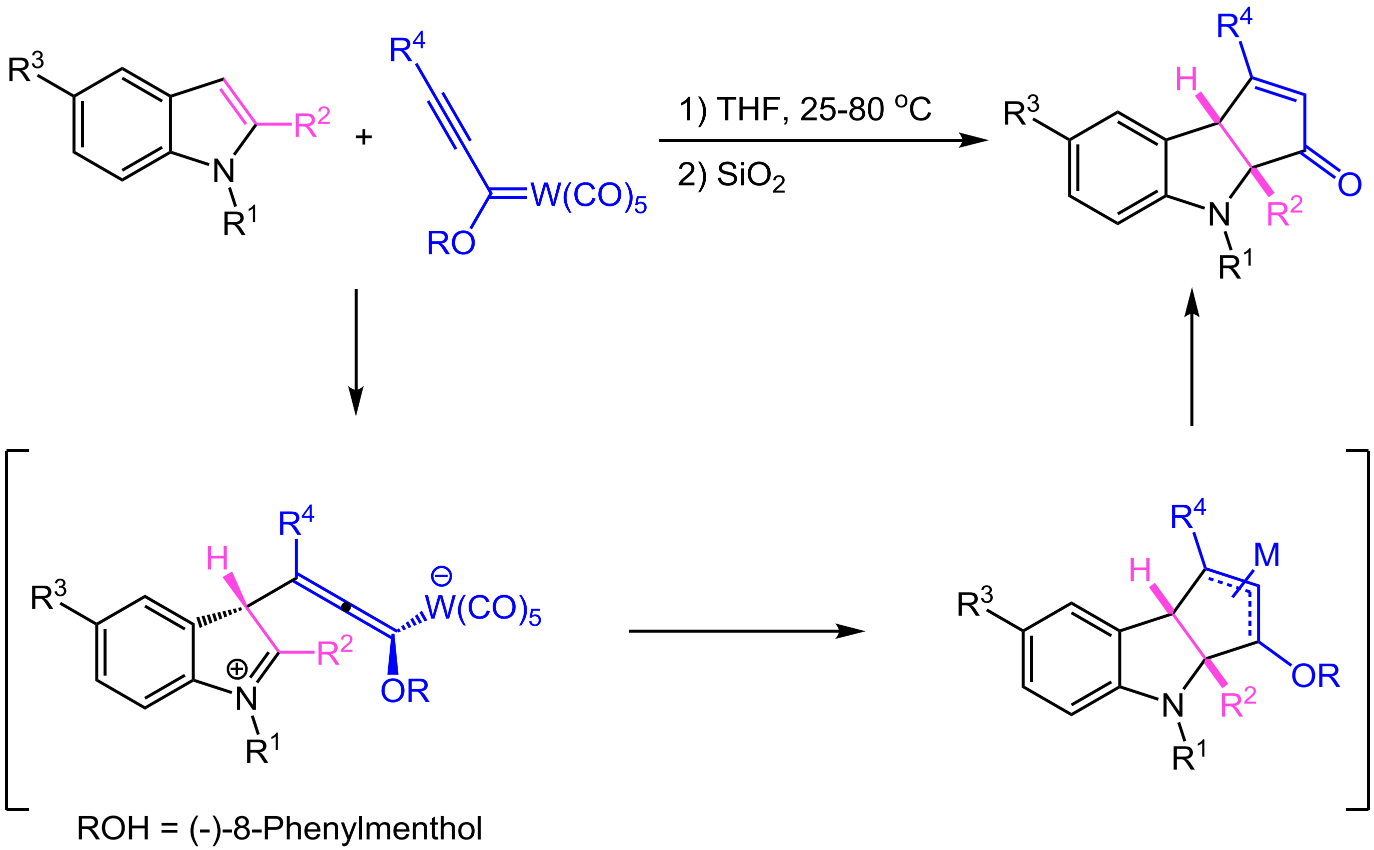


72% yield

Origin of Stereochemical Control

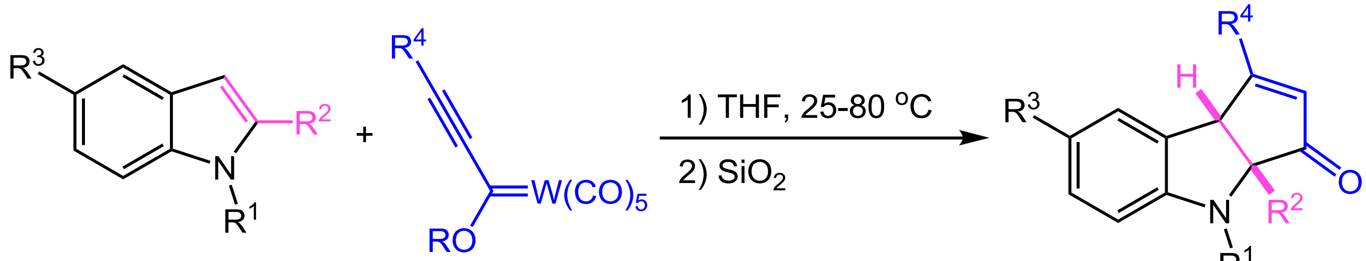


Asymmetric (3+2) Cycloaddition of Indole with Carbenes

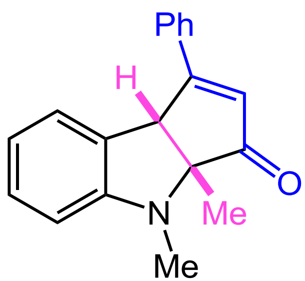


Tomás, M. *et al*. *J. Am. Chem. Soc.* **2009**, *131*, 2096.

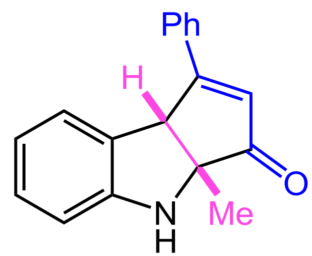
Substrate Scope



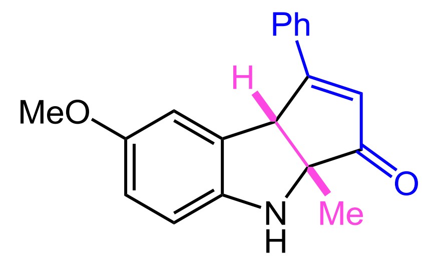
ROH = (-)-8-Phenylmenthol



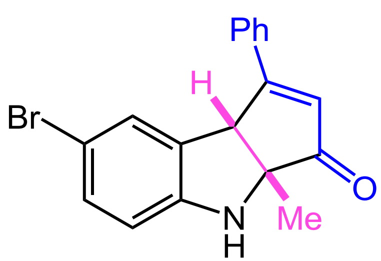
50% yield, 97% ee



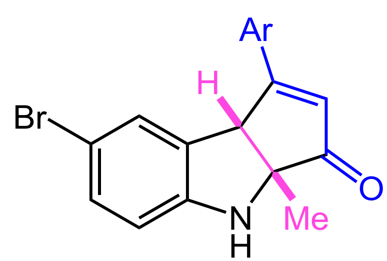
69% yield, >99% ee



70% yield, >99% ee

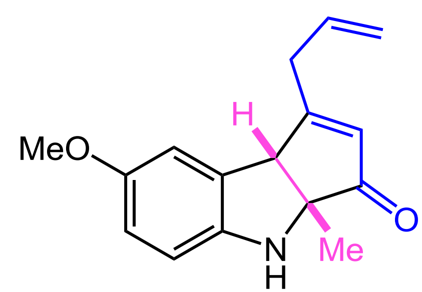


52% yield, >99% ee



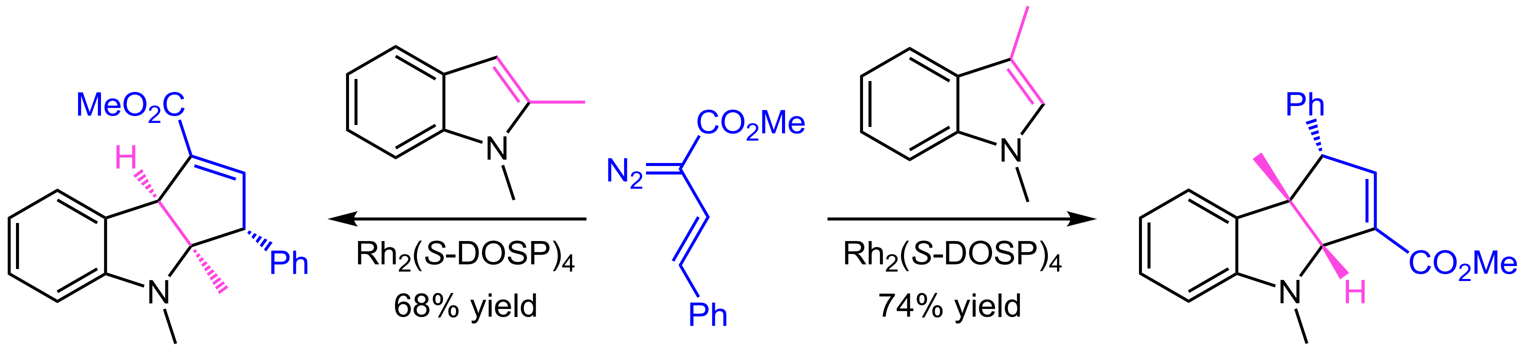
Ar = 4-Cl-C_6H_4

45% yield, >99% ee



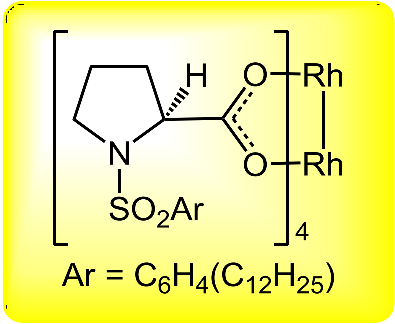
67% yield, >99% ee

Rhodium-Catalyzed (3+2) Cycloaddition of Indole



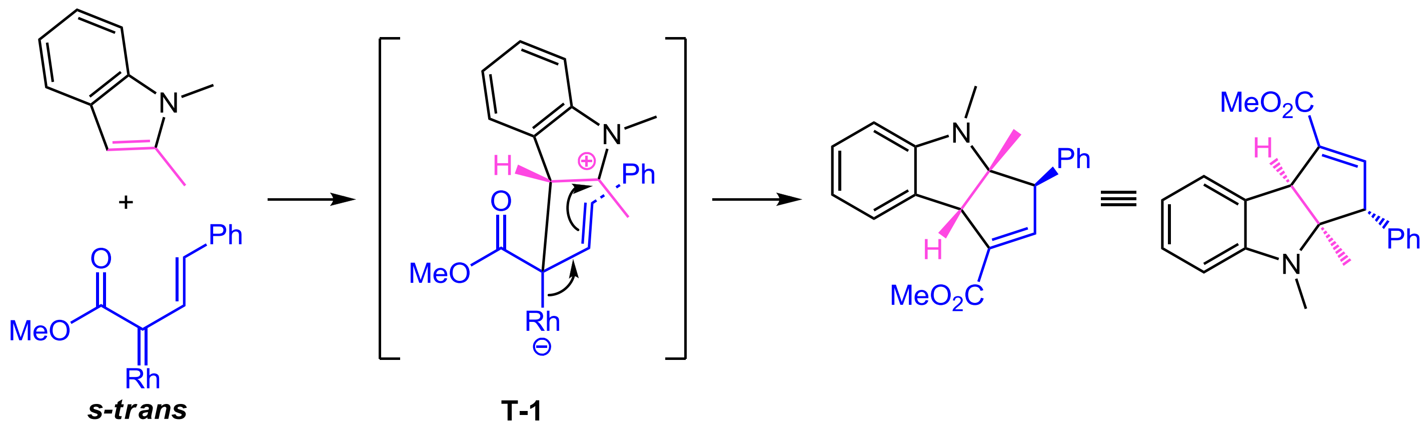
>30:1 dr, 97% ee

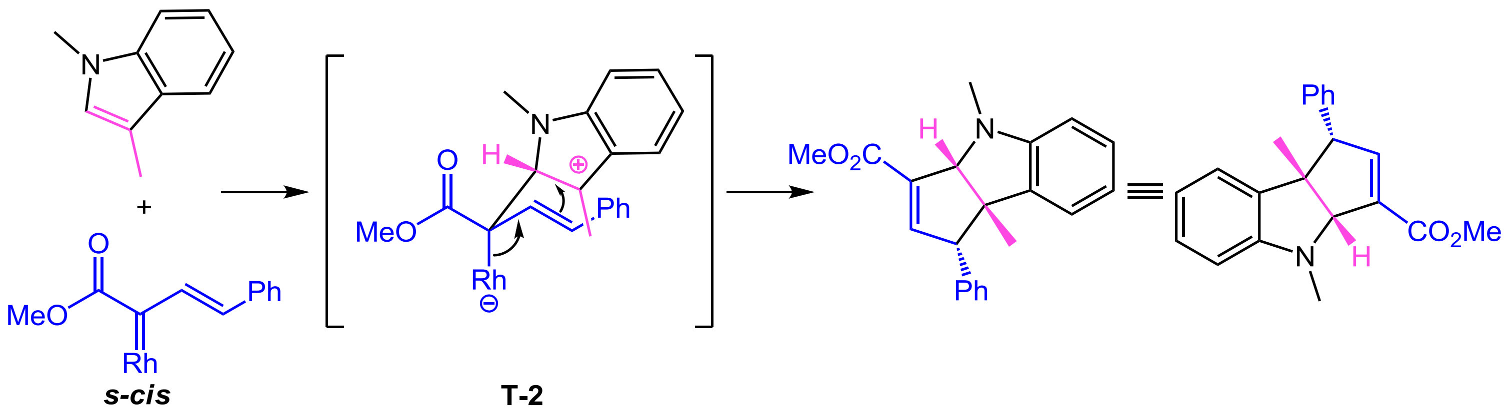
>30:1 dr, 99% ee



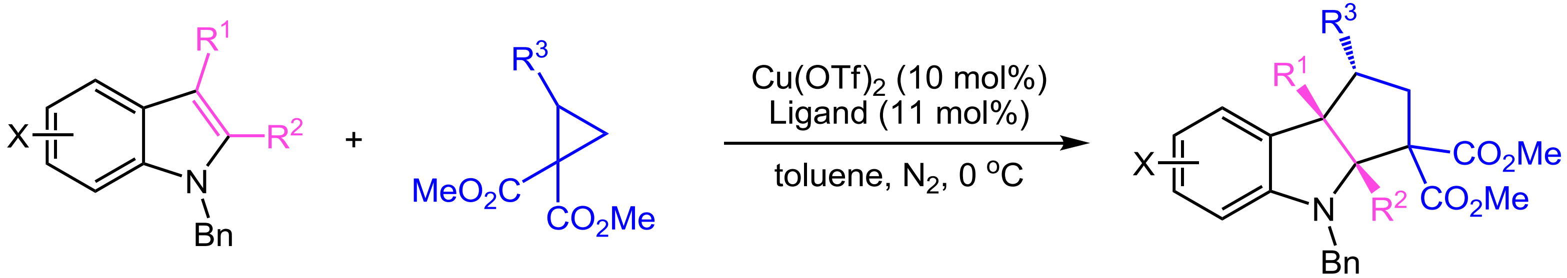
Davies, H. M. L. *et al*. *J. Am. Chem. Soc.* **2010**, *132*, 440.

Proposed Reaction Mechanism

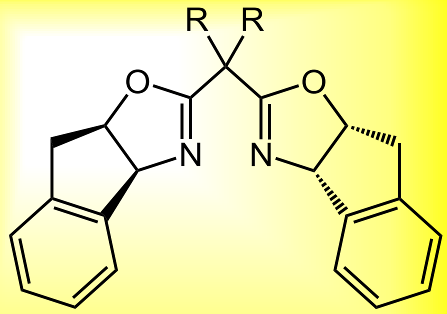




Copper-Catalyzed (3+2) Cycloaddition of Indole



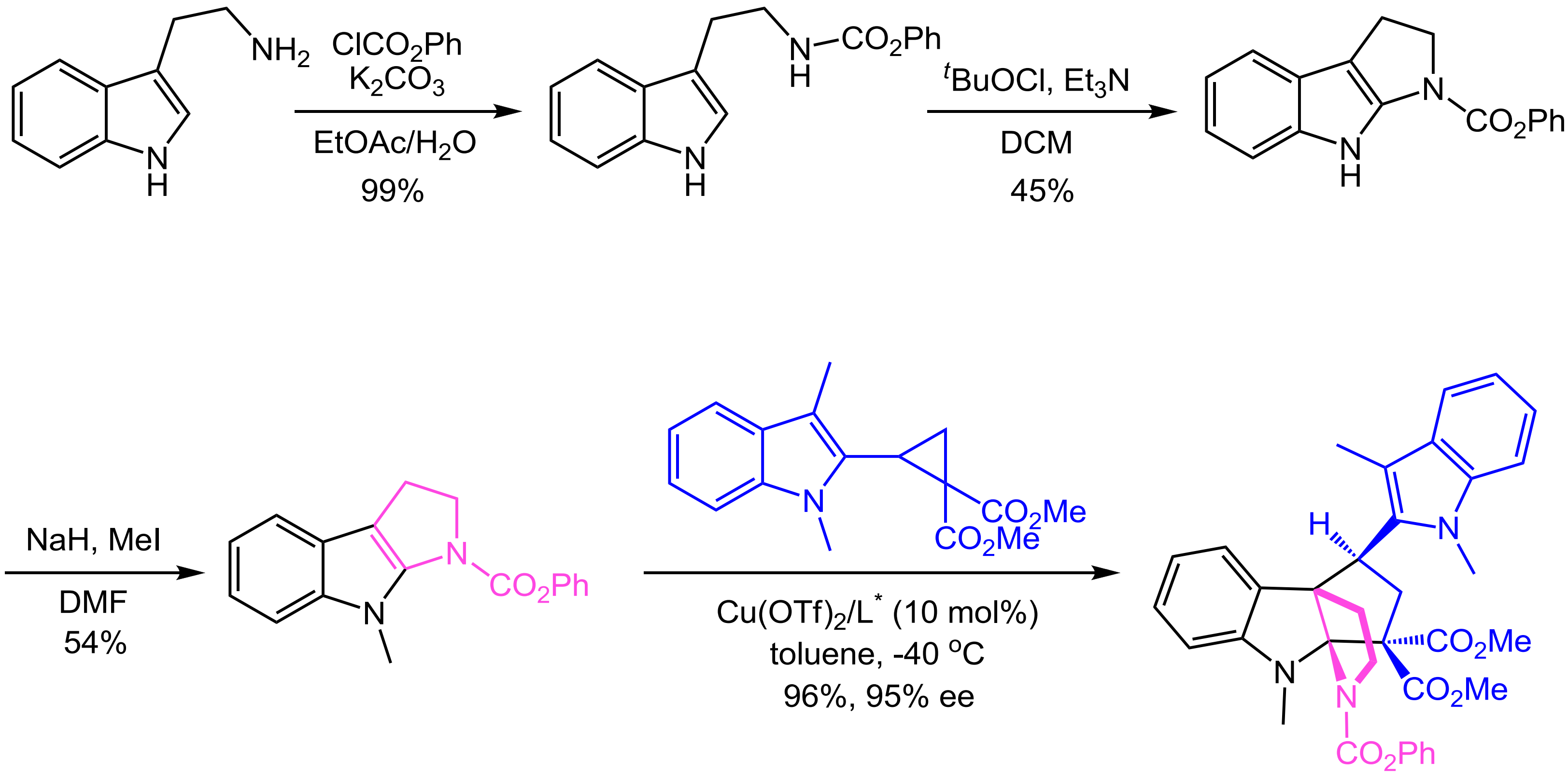
up to >50:1 dr, 96% ee



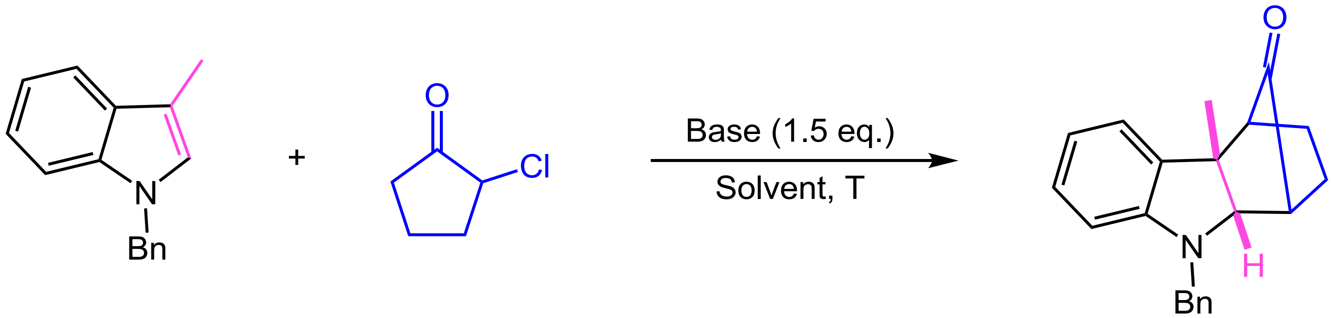
R = 3,5-^{t}$Bu_2C_6H_3CH_2$

Tang, Y. *et al*. *J. Am. Chem. Soc.* **2013**, *135*, 7851.

Synthesis of the Core of Borreverine



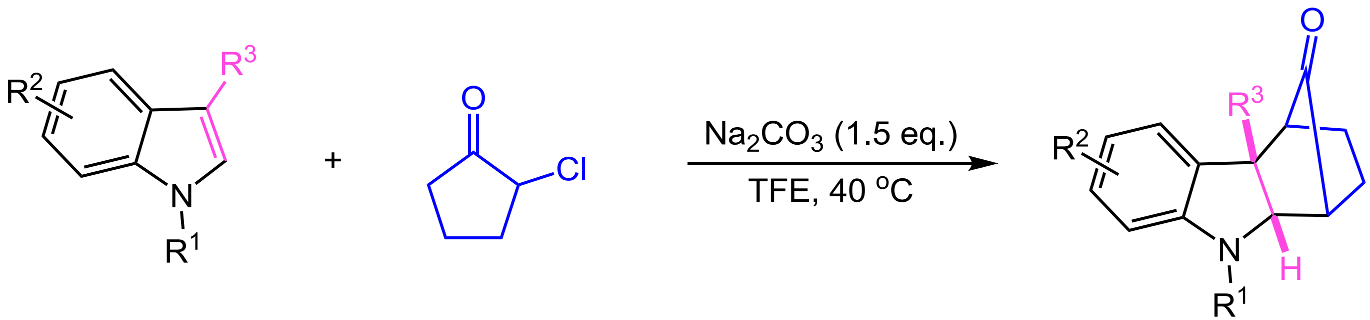
(3+2) Cycloaddition of Indole with α-Haloketones

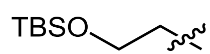
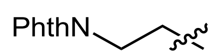
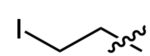


Entry	Base	Solvent	Concn (M)	T (°C)	Yield (%)	Dr
1	Na_2CO_3	MeOH	0.5	rt	23	12:1
2	Na_2CO_3	TFE	0.5	rt	71	6:1
3	Na_2CO_3	TFE	1	rt	79	5:1
4	Et_3N	TFE	1	rt	48	4.6:1
5	DIPEA	TFE	1	rt	71	6.7:1
6	DMAP	TFE	1	rt	51	4.6:1
7	**Na_2CO_3**	**TFE**	**1**	**40**	**93**	**6:1**

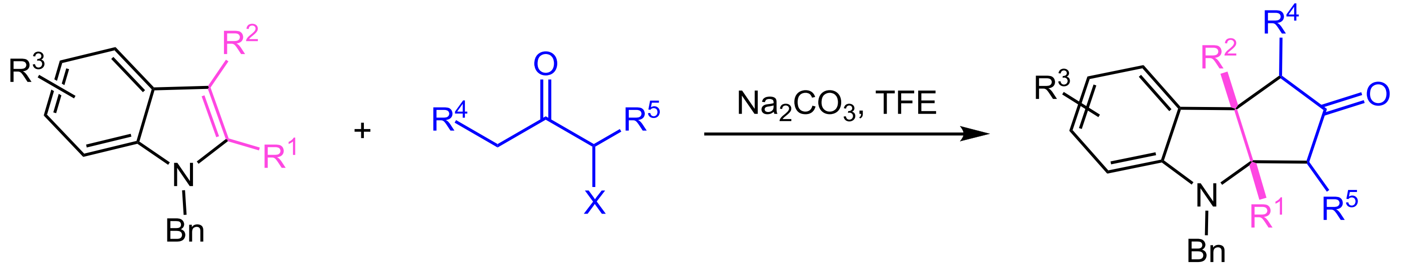
Wu, J. *et al*. *J. Am. Chem. Soc.* **2014**, *136*, 6288.

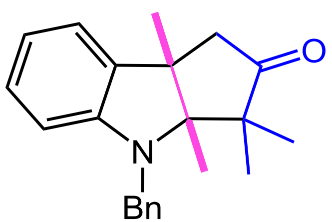
Substrate Scope



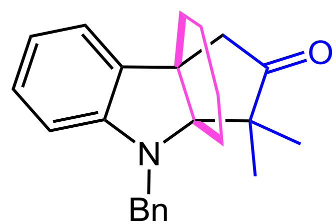
Entry	R^1	R^2	R^3	Yield (%)	Dr
1	Bn	H	^{i}Pr	87	11:1
2	Bn	H	cyclohexyl	84	18:1
3	Bn	H	allyl	83	11:1
4	Bn	H		74	13:1
5	Bn	H		87	10:1
6	Bn	5-Cl	^{i}Pr	91	32:1
7	Me	H	cyclohexyl	82	16:1
8	Me	H		88	4.5:1
9	allyl	H	Me	79	7.5:1

Substrate Scope

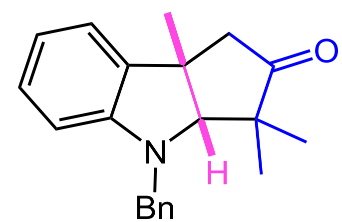




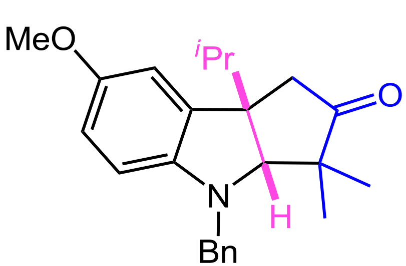
X = Br, 81% yield



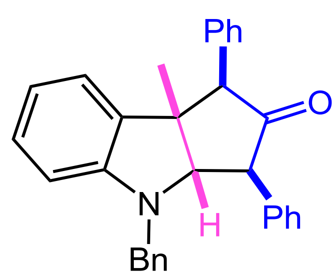
X = Br, 77% yield



X = Br, 76% yield

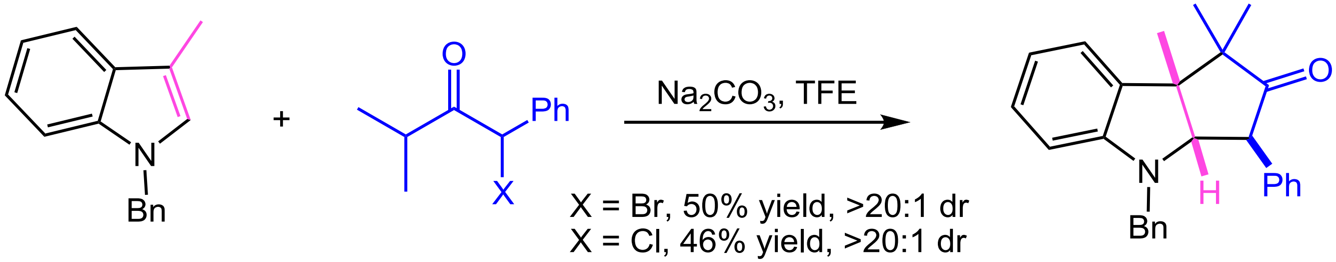


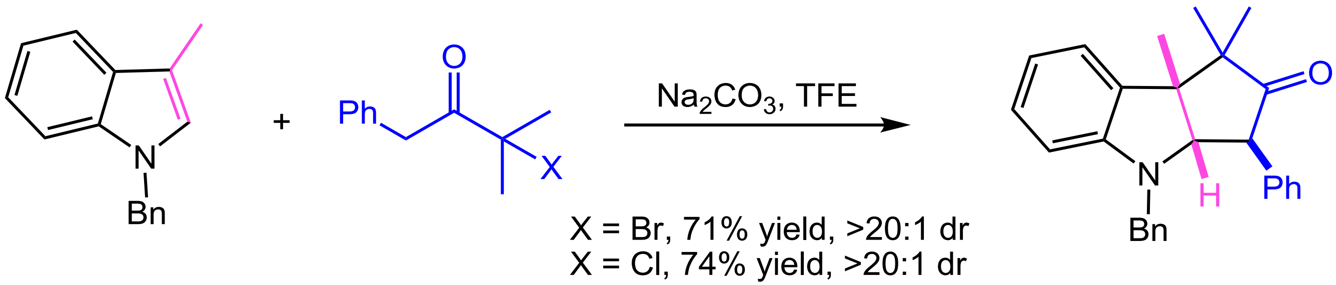
X = Br, 72% yield

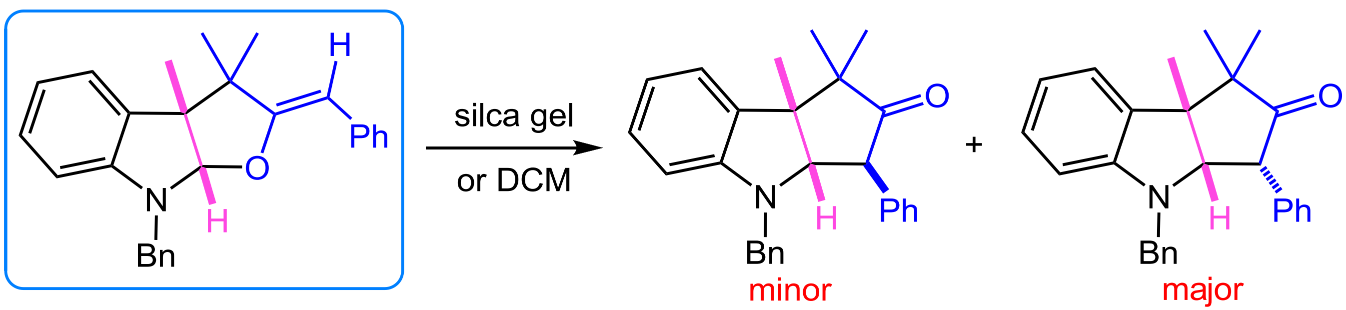


X = Cl, 47% yield

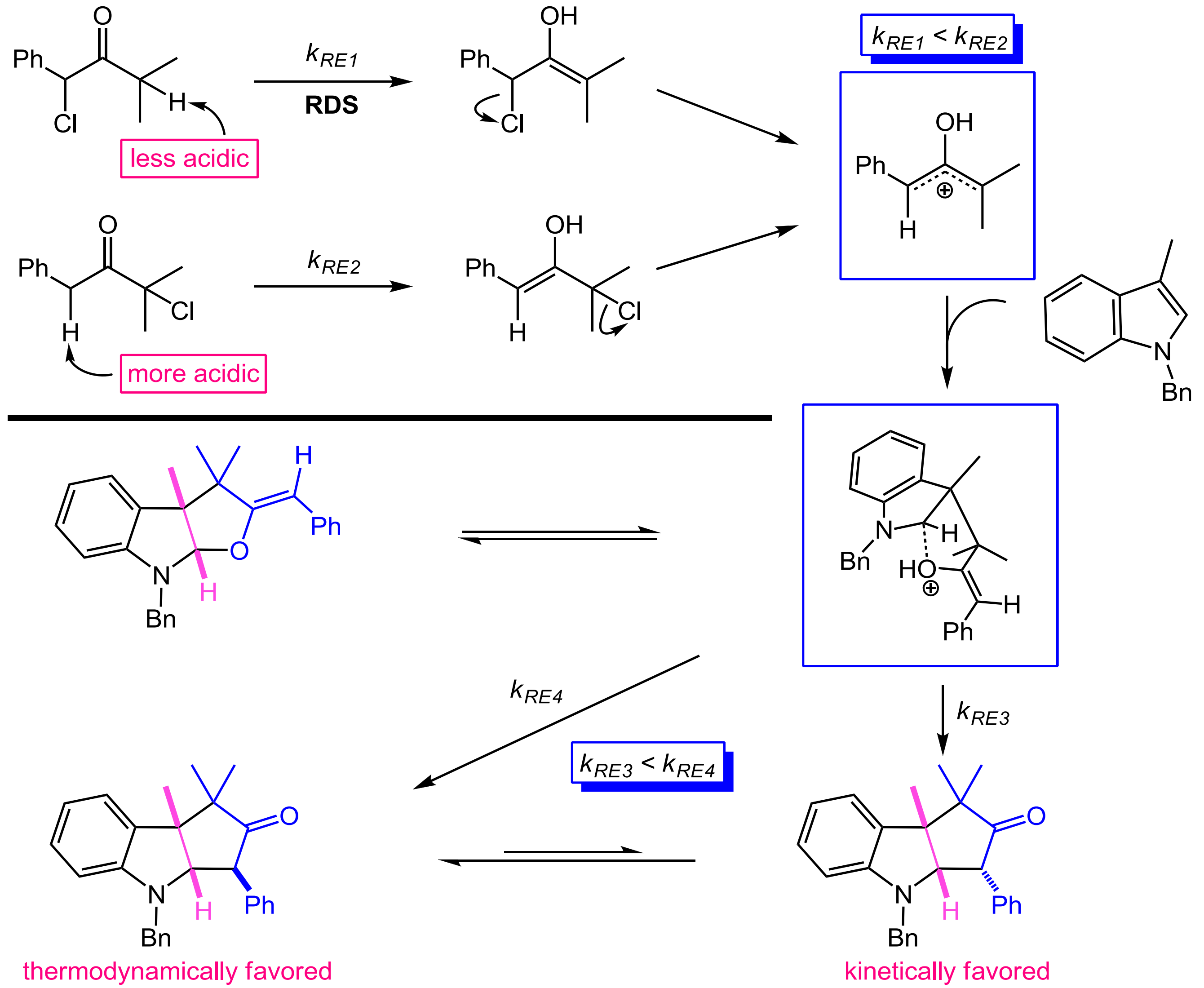
Substrate Scope



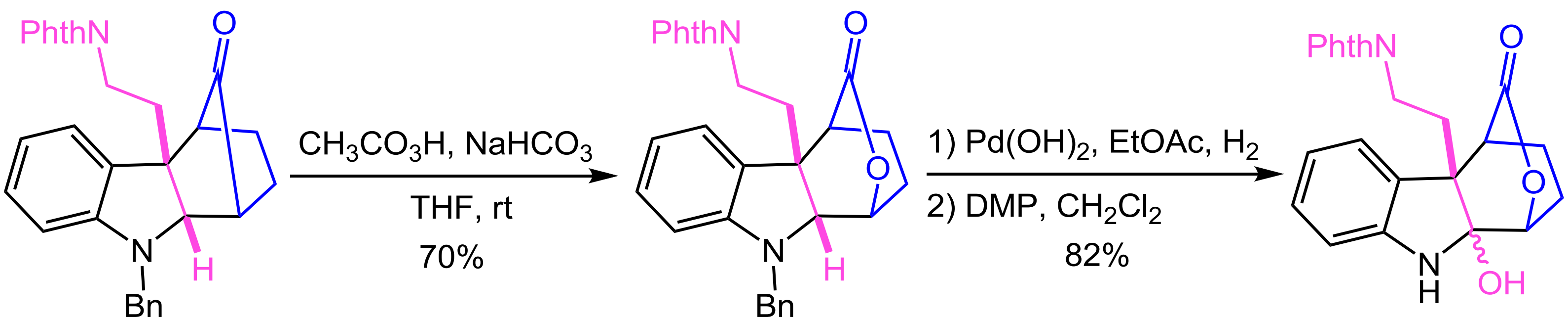


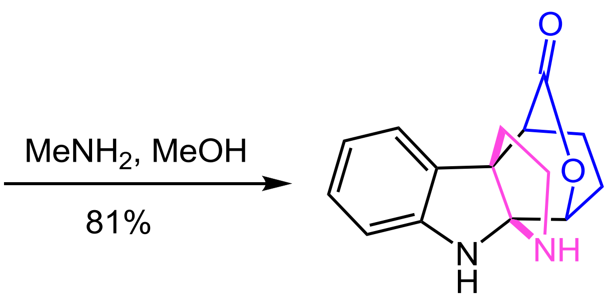


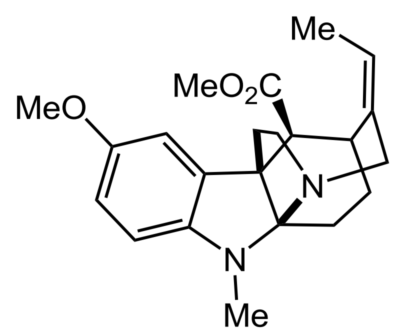
Proposed Reaction Mechanism



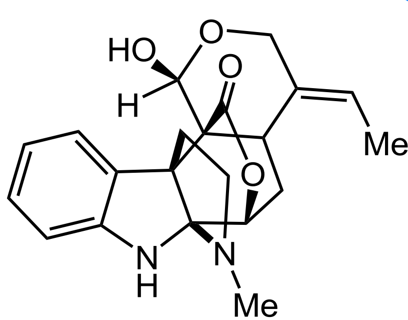
Synthesis of the Core of Vincorine and Isocorymine







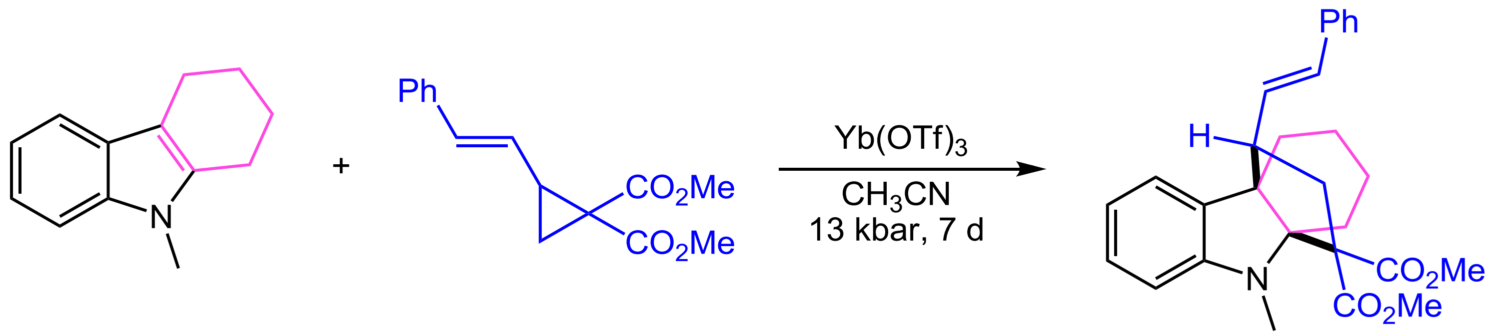
Vincorine



Isocorymine

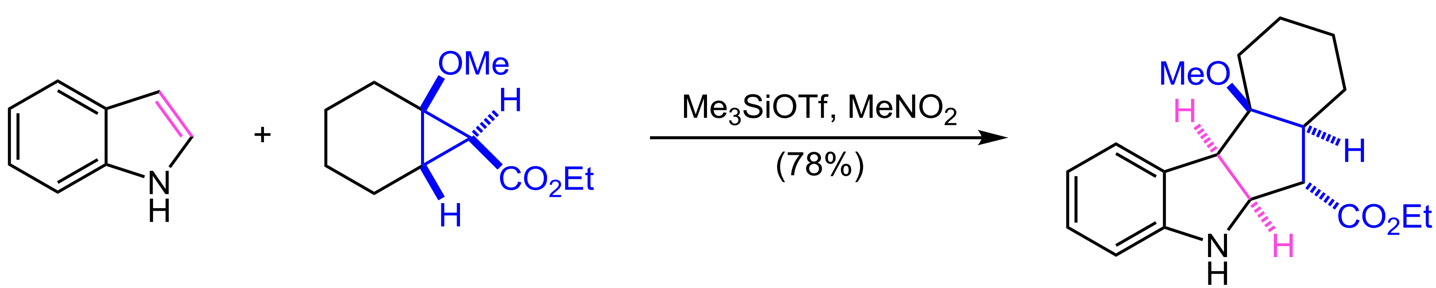
Summary

Kerr: (3+2) cycloaddition of indole with 1,1-cyclopropane diesters



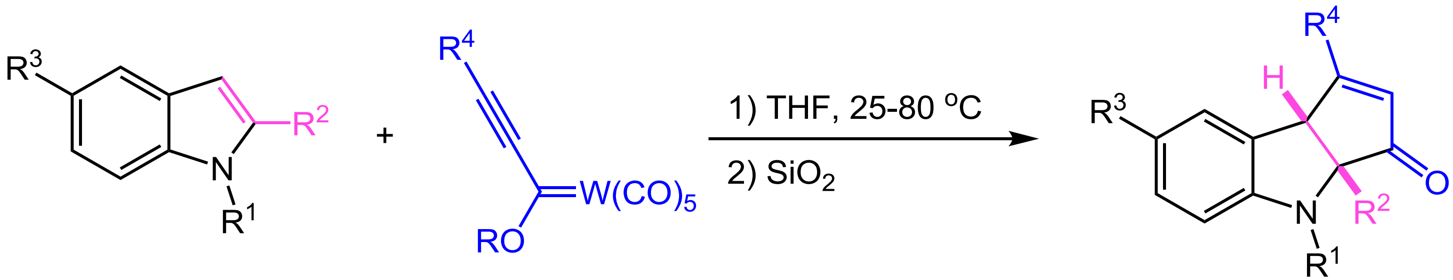
49% yield, 3:1 dr

Pagenkopf: (3+2) cycloaddition of Indole with 2-alkoxycyclopropanoate esters



Summary

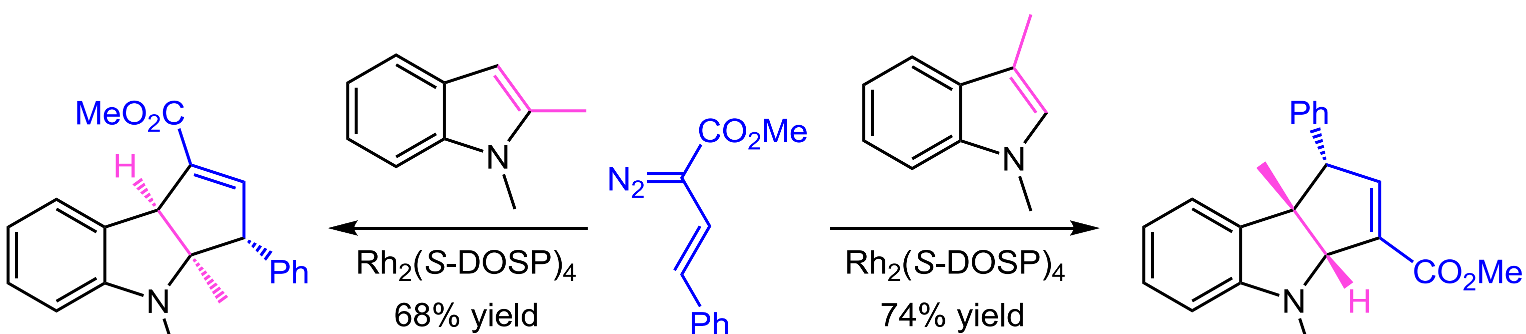
Tomas: asymmetric (3+2) cycloaddition of indole with carbenes



ROH = (-)-8-Phenylmenthol

up to 70% yield, >99% ee

Davies: Rhodium-catalyzed (3+2) cycloaddition of indole

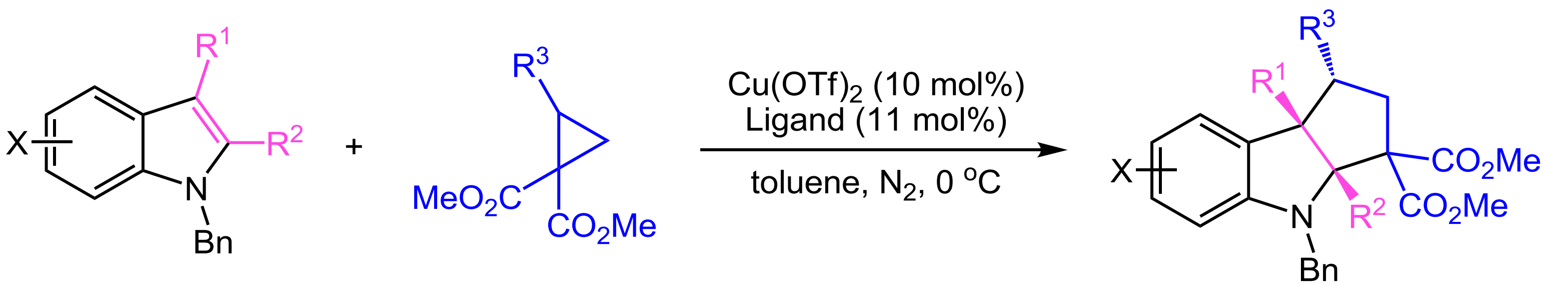


>30:1 dr, 97% ee

>30:1 dr, 99% ee

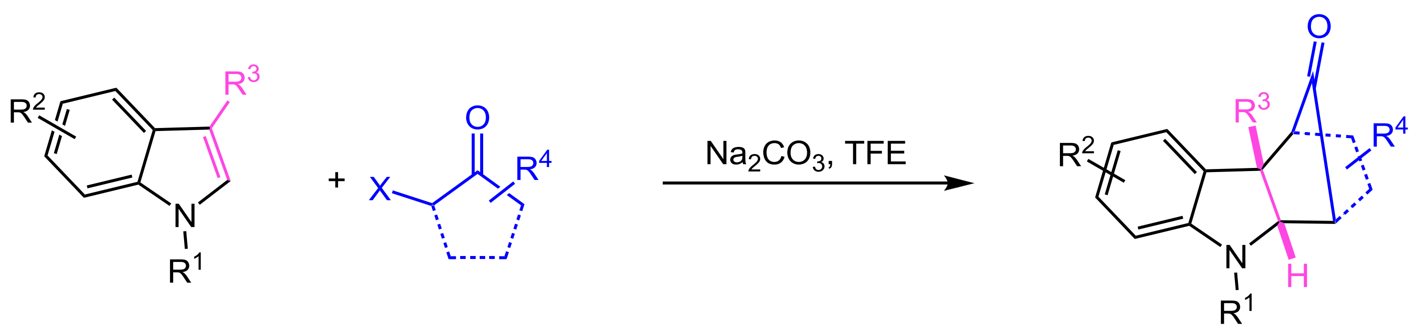
Summary

Tang: Copper-catalyzed (3+2) cycloaddition of indole



up to >50:1 dr, 96% ee

Wu: (3+2) cycloaddition of indole with α-haloketones



Dearomatization of indoles has been a powerful strategy for organic chemists to access many architecturally complex alkaloids. Due to the ubiquitous nature of the indole unit in important bioactive alkaloids, numerous chemo-, regio-, and enantioselective methodologies have emerged. Some dearomative strategies include allylation, alkylation, arylation, iminium catalysis, and cycloaddition. Dearomative cycloaddition, which is based on the reactivity of the C2=C3 double bond of indole, is an attractive and straightforward approach to fused indoline compounds. Moreover, indolines with a fused five- or six-membered ring at the C2 and C3 positions are well represented in nature.

The dearomatization of the C2/C3 double bond of 3-substituted indoles with *α*-haloketones has been reported. Both high efficiency and high diastereocontrol were observed in the majority of cases. DFT calculations suggest that the preferred mechanism for the formal cycloaddition may proceed *via* hydroxyallyl cations rather than the corresponding oxyallyl cations. *O*-Alkylated intermediates are initially formed, followed by isomerization to the observed products. The synthetic potential of this dearomatization process was demonstrated by concise syntheses of the core structures of vincorine, iso-corymine, and aspidophylline A. With an eye toward targeting malagashanine, efforts are ongoing in our laboratory to obtain regioisomeric lactone **37**.