Catalytic Enantioselective Synthesis of Functionalized Tropanes

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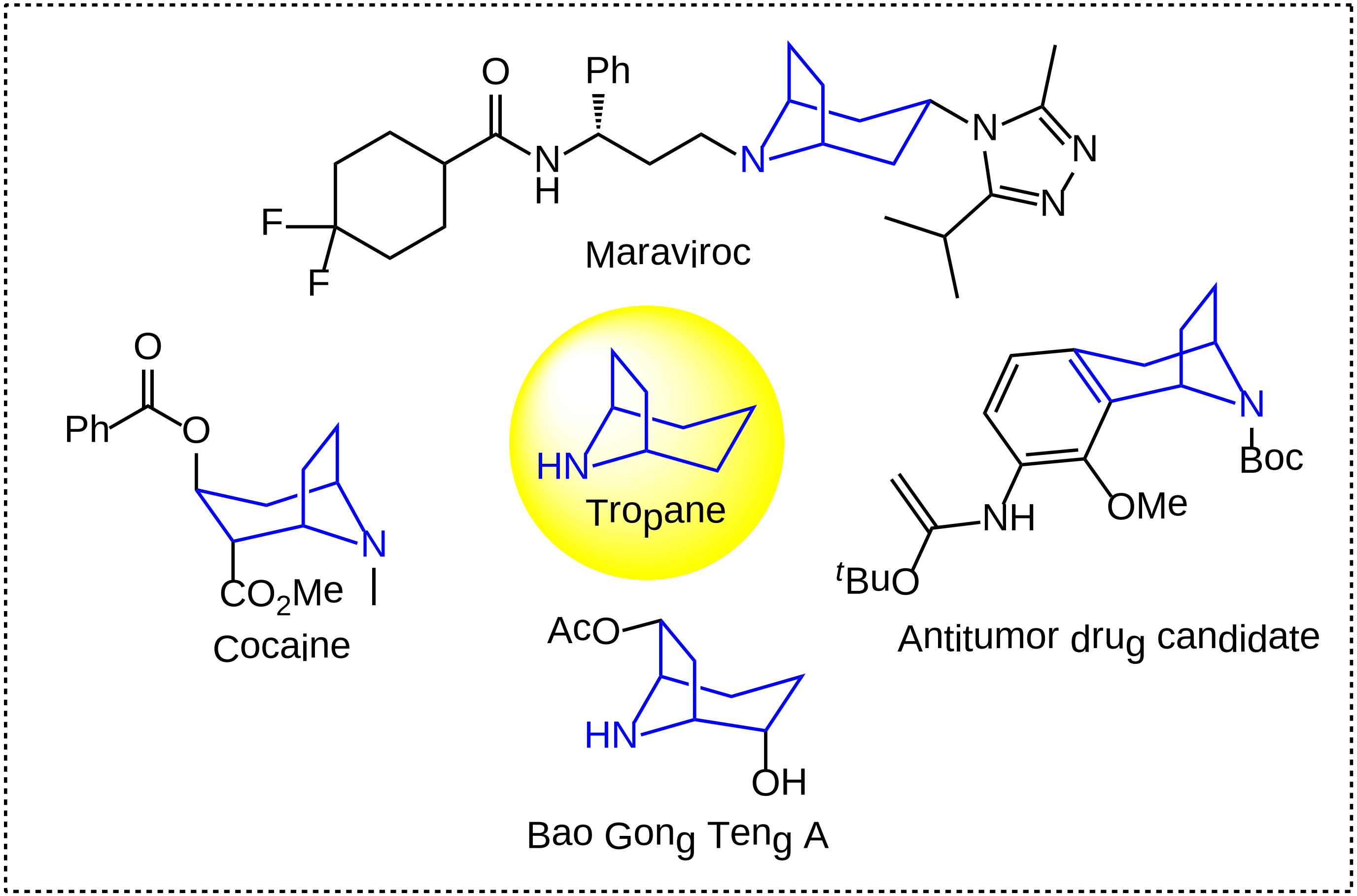
Checker: Shubo Hu

Date: 2016-11-07

Xu, J.-H., Zheng, S.-C., Zhang, J.-W. Liu, X.-Y., Tan, B.
Angew. Chem. Int. Ed. **2016**, *55*, 11834.

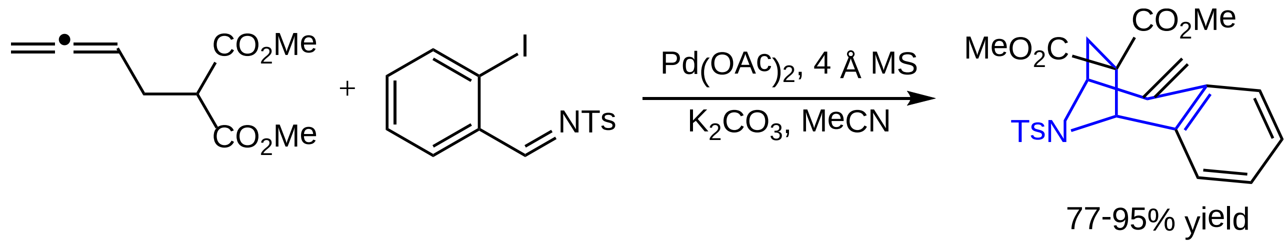
Contents

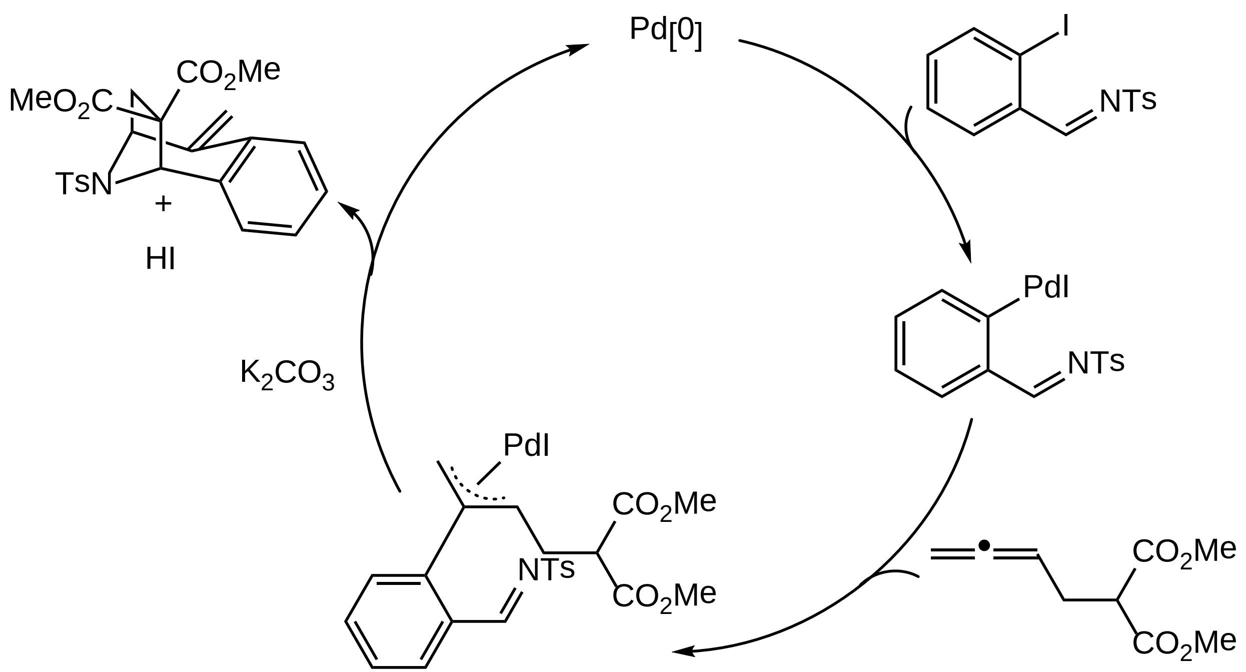
Introduction



Carroll, F. I. *et al. J. Med. Chem*. **2004**, *47*, 6401.
Haycock-Lewandowski *et al. Org. Process Res. Dev*. **2008**, *12*,1094.

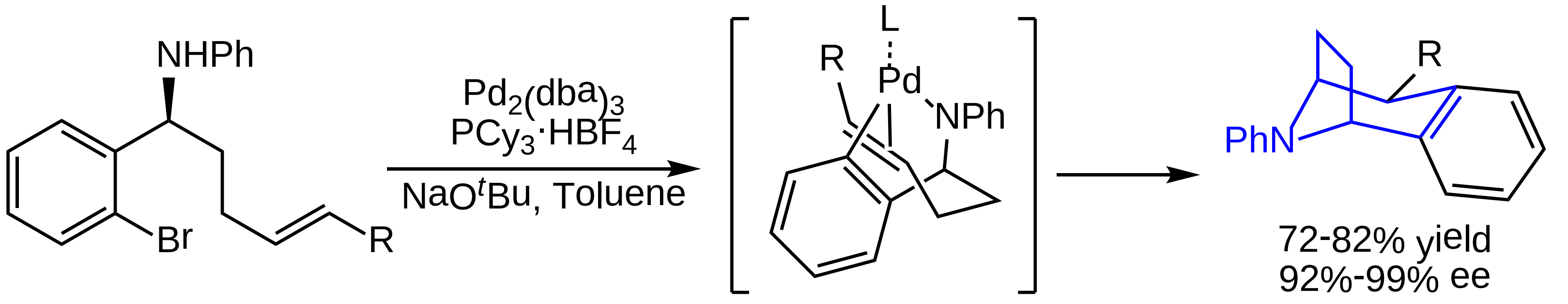
Introduction





Ma, S. *et al. Org. Lett*. **2011**, *13*, 466.

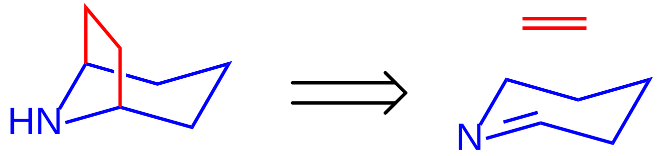
Introduction



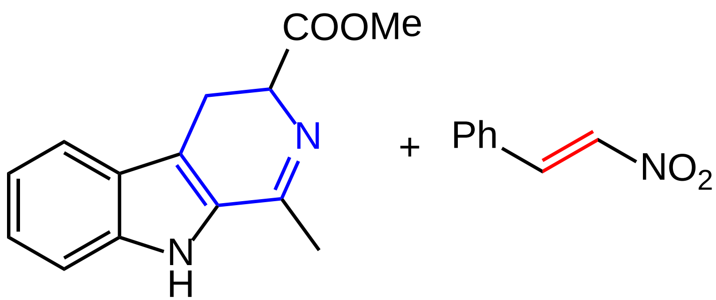
Wolfe, J. P. *et al. Org. Lett*. **2011**, *13*, 2962.

The strategies

The retrosynthetic analysis:

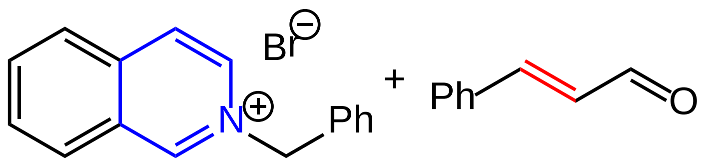


Strategy one:



[3+2] cycloaddition reaction
metal catalyst involved (Cu)

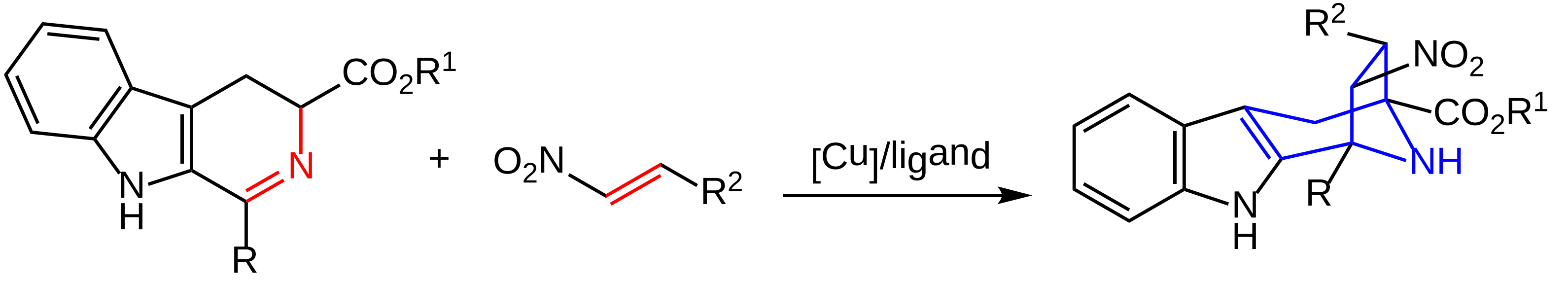
Strategy two:



dearomatization of isoquinoline
metal-free organocatalyst (NHC)

Waldmann, H. *et al*. *Angew. Chem. Int. Ed*. **2013**, *52*, 12892.
Tan, B. *et al. Angew. Chem. Int. Ed*. **2016**, *55*, 11834.

[3+2] cycloaddition reaction



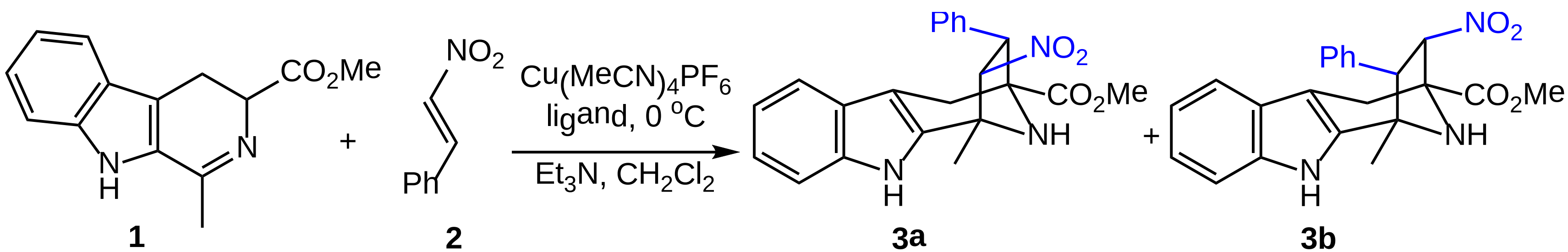
1,3-Fused azomethine ylide

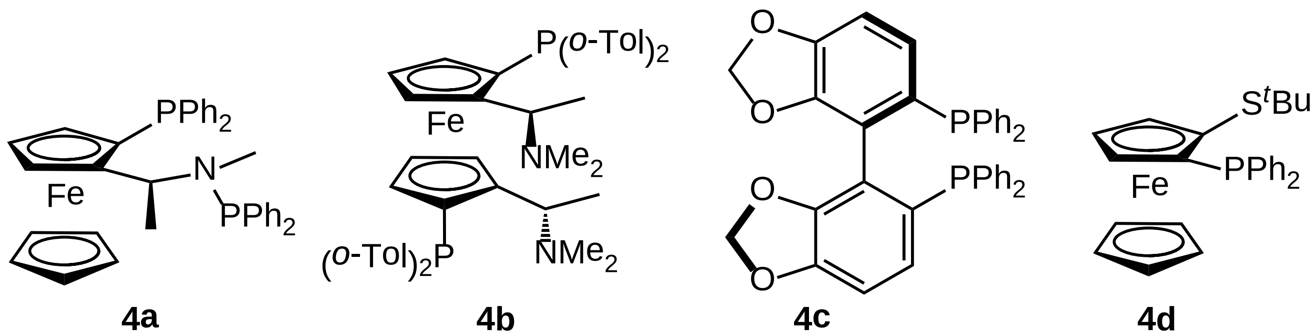
R^2 = Alkyl or Aryl

62-96% yield
78-96% ee

Waldmann, H. *et al*. *Angew. Chem. Int. Ed*. **2013**, *52*, 12892.

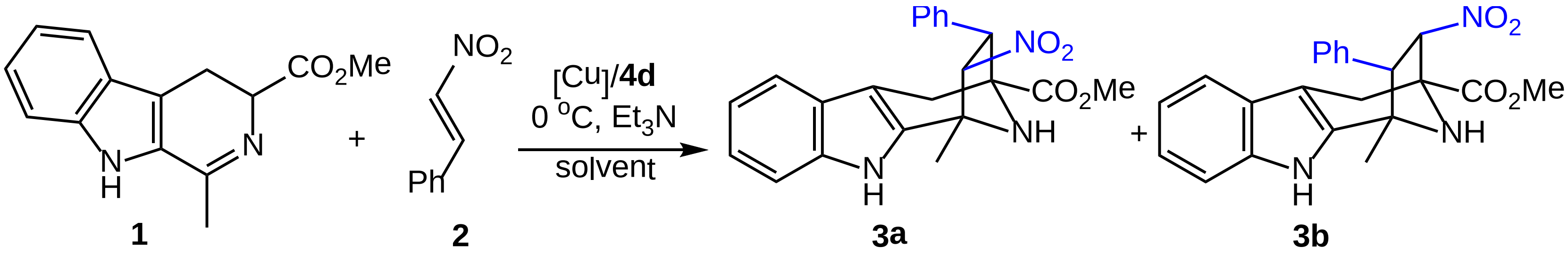
Ligand effect





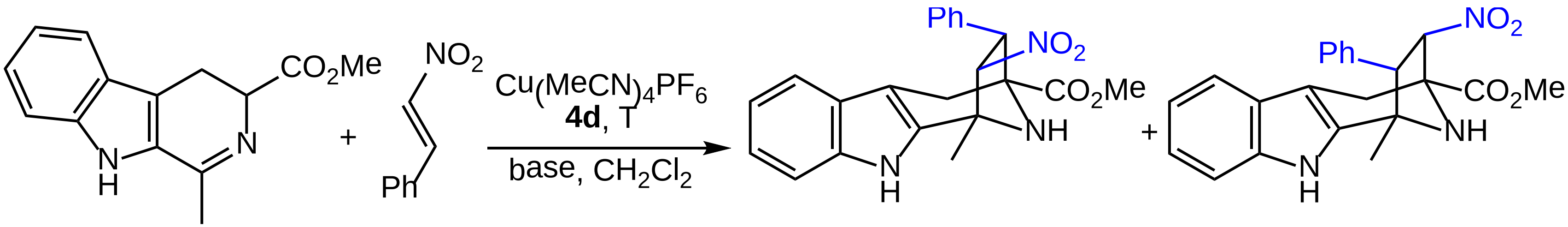
entry	ligand	yield (%)	dr	ee (%)
1	**4a**	46	6:5	19
2	**4b**	56	11:5	47
3	**4c**	41	4:5	87
4	**4d**	**69**	**>20:1**	**86**

Solvent and metal effect



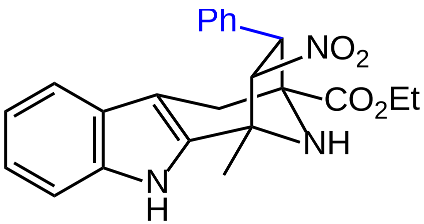
entry	solvent	[Cu]	yield (%)	dr	ee (%)
1	**CH_2Cl_2**	**$Cu(MeCN)_4PF_6$**	**69**	**>20:1**	**86**
2	PhMe	$Cu(MeCN)_4PF_6$	52	>20:1	55
3	Et_2O	$Cu(MeCN)_4PF_6$	43	>20:1	69
4	CH_3CN	$Cu(MeCN)_4PF_6$	79	>20:1	70
5	CH_2Cl_2	$Cu(MeCN)_4BF_4$	64	>20:1	74
6	CH_2Cl_2	$Cu(MeCN)_4ClO_4$	67	>20:1	75
7	CH_2Cl_2	CuOTf·PhMe	51	>20:1	68

Base effect

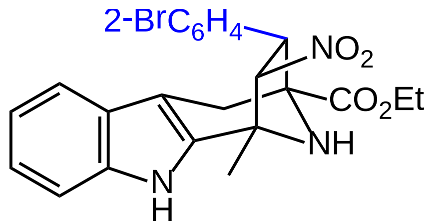


entry	base	T (°C)	yield (%)	dr	ee (%)
1	Et_3N	0	69	>20:1	86
2	DIPEA	0	21	>20:1	33
3	DBU	0	77	>20:1	87
4	KO*t*Bu	0	26	>20:1	77
5	**DBU**	**-20**	**87**	**>20:1**	**86**
6	DBU	-75	77	>20:1	86

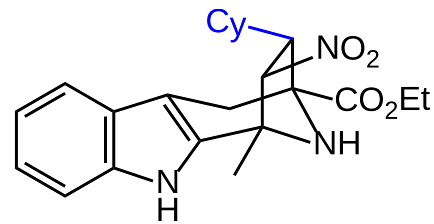
Substrate Scope



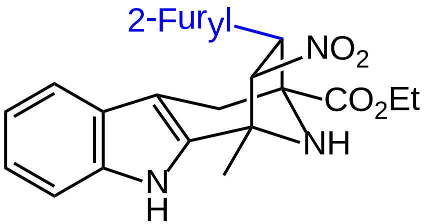
75% yield, 87% ee



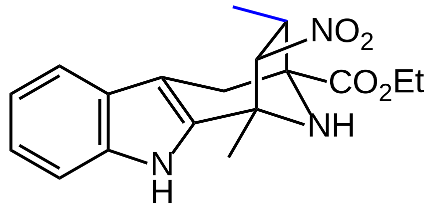
76% yield, 86% ee



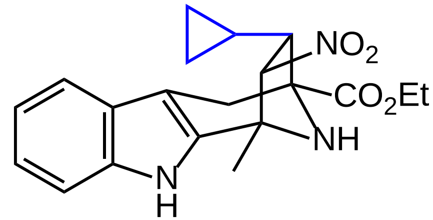
75% yield, 96% ee



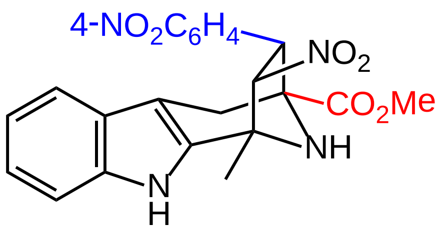
80% yield, 84% ee



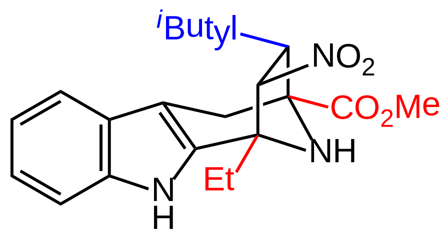
75% yield, 87% ee



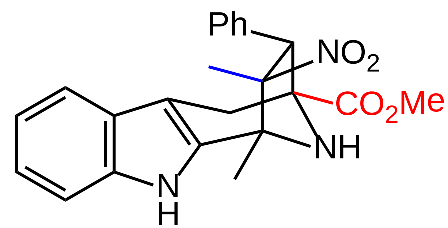
86% yield, 91% ee



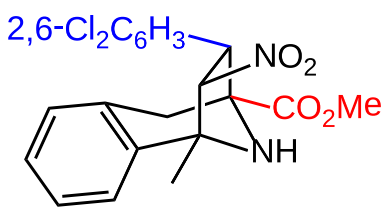
66% yield, 87% ee



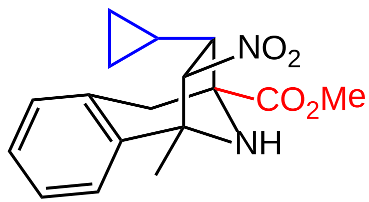
76% yield, 85% ee



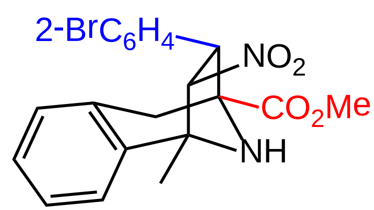
62% yield, 78% ee



89% yield, 86% ee

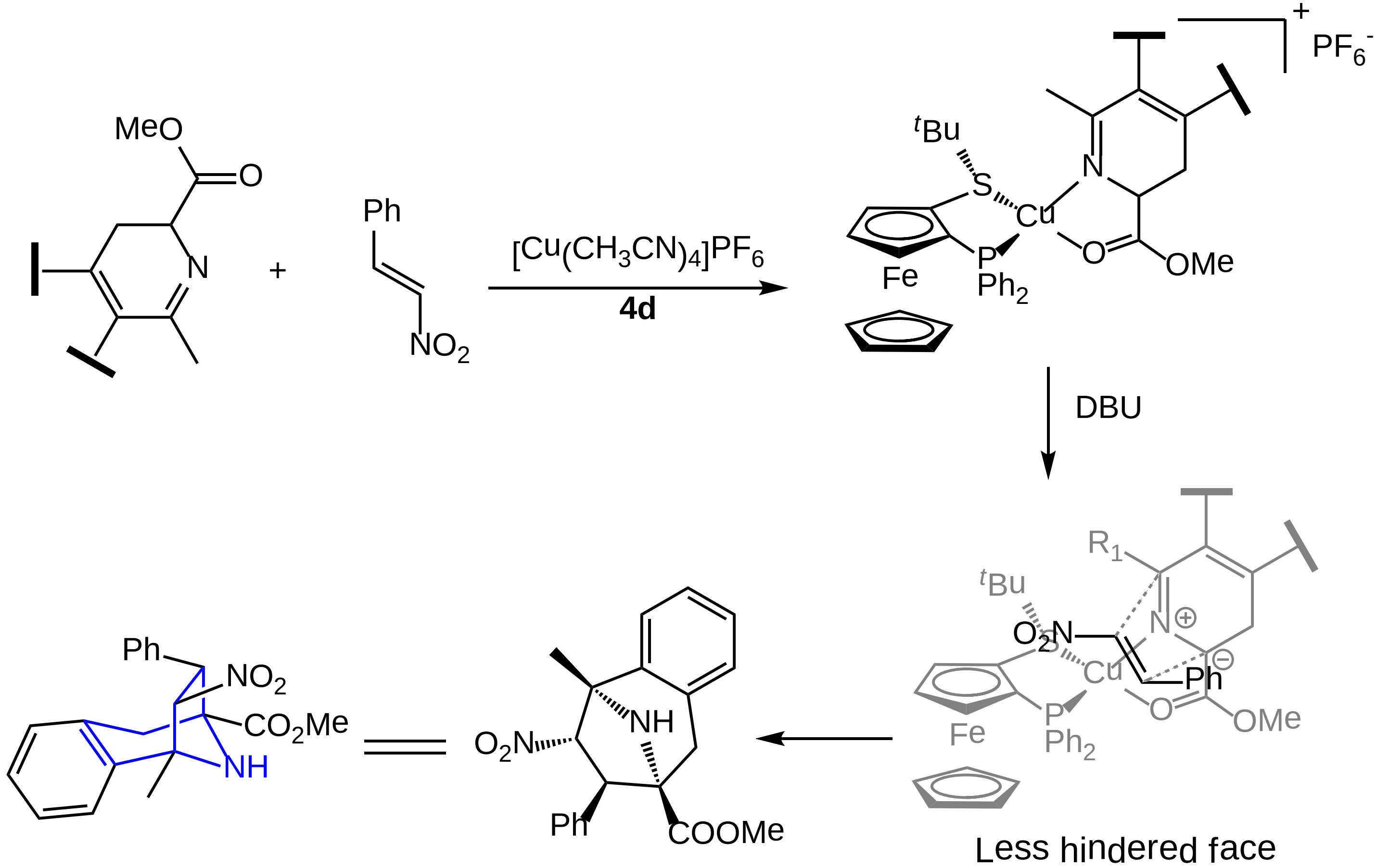


66% yield, 91% ee

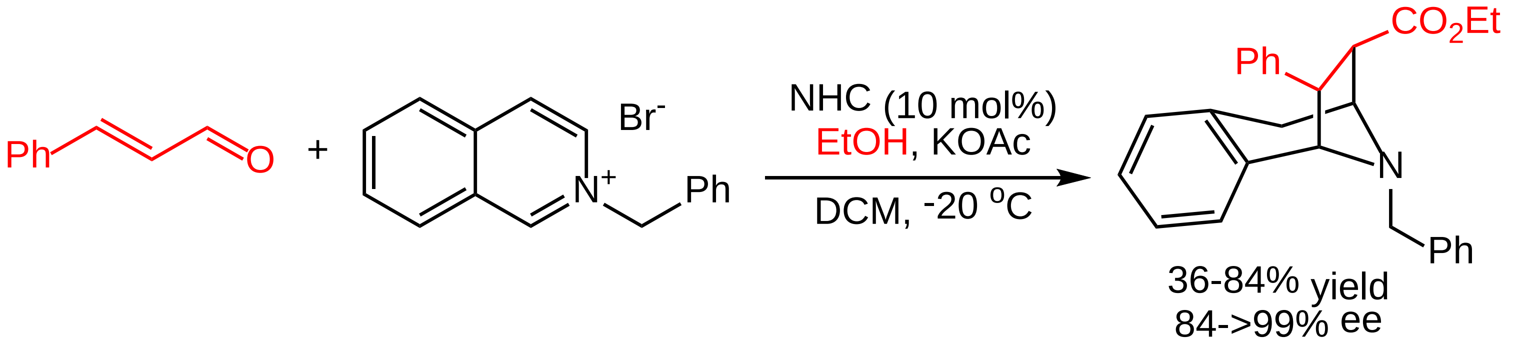


96% yield, 87% ee

Proposed mechanism

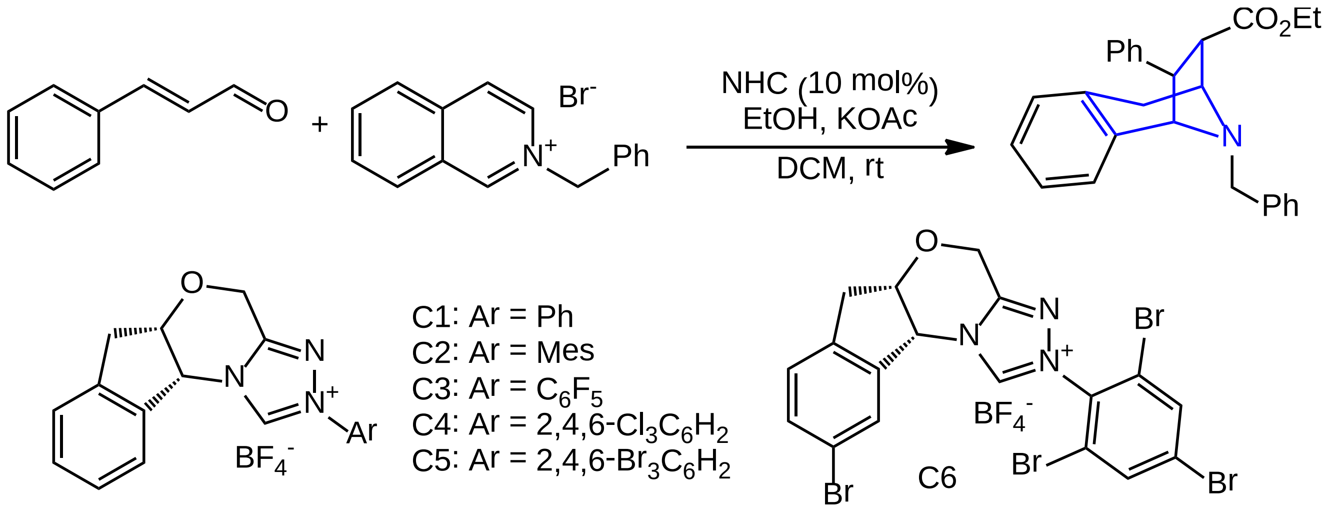


Dearomatization reaction



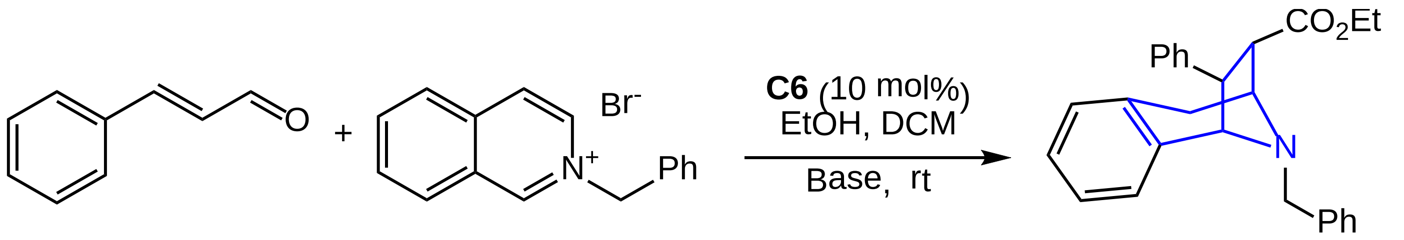
Tan, B. *et al. Angew. Chem. Int. Ed*. **2016**, *55*, 11834.

NHC organocatalyst screening



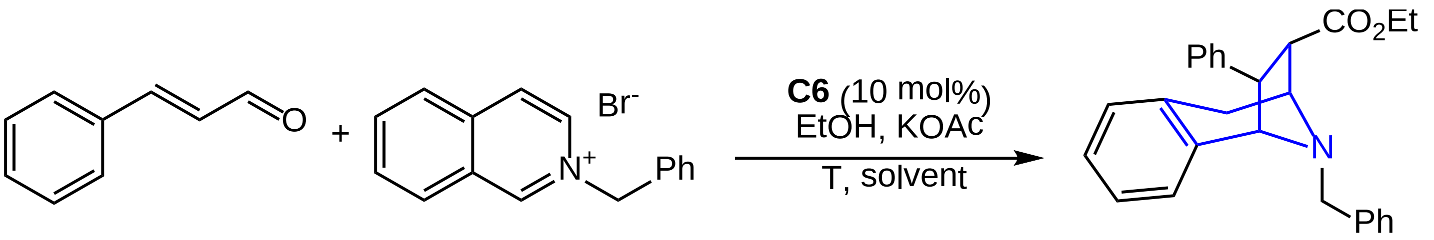
entry	NHC	yield (%)	dr	ee (%)
1	C1	39	>20:1	48
2	C2	6	>20:1	27
3	C3	18	>20:1	60
4	C4	39	>20:1	88
5	C5	30	>20:1	91
6	**C6**	**42**	**>20:1**	**90**

Base effect



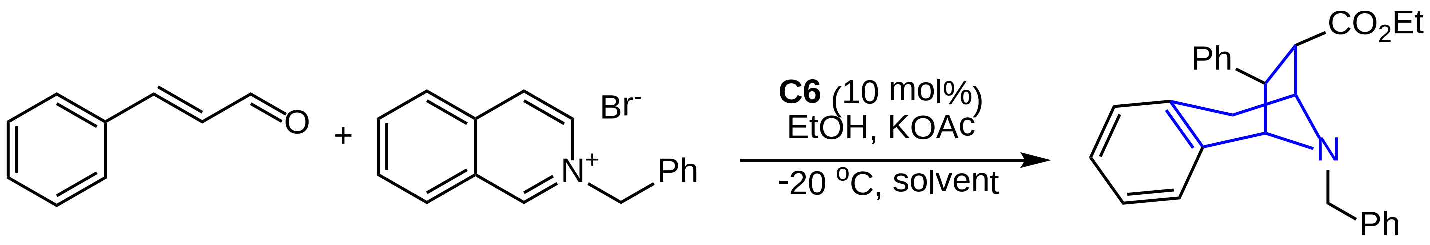
entry	Base	yield (%)	dr	ee%
1	NaOAc	10	>20:1	53
2	K_2CO_3	21	>20:1	79
3	Et_3N	36	>20:1	75
4	DIPEA	35	>20:1	79
5	DBU	Trace	>20:1	Not determined
6	DABCO	Trace	>20:1	Not determined
7	**KOAc**	**42**	**>20:1**	**90**

Temperature and solvent effect



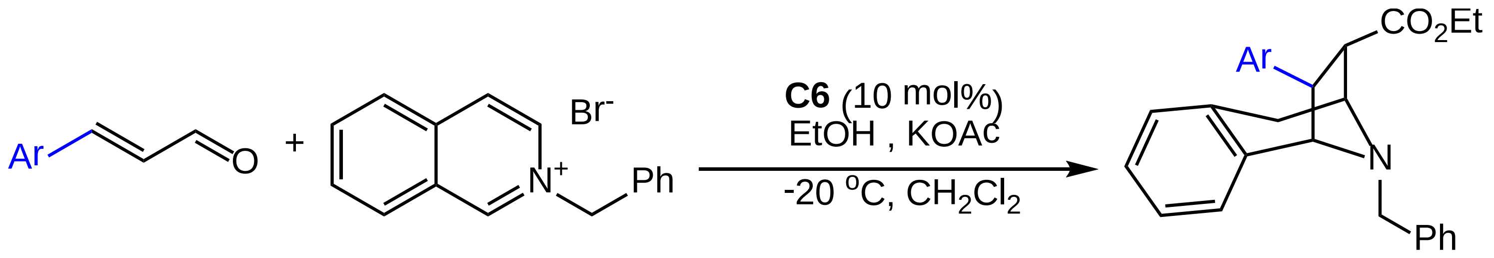
entry	T (°C)	solvent	yield (%)	dr	ee %
1	rt	DCM	42	>20:1	90
2	0	DCM	49	>20:1	92
3	**-20**	**DCM**	**57**	**>20:1**	**93**
4	-20	EtOH	58	>20:1	89
5	-20	toluene	30	>20:1	82
6	-20	$CHCl_3$	50	>20:1	85

KOAc and EtOH effect



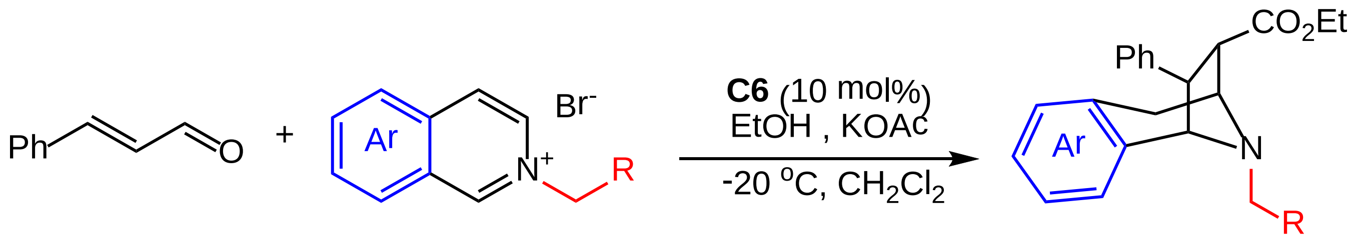
entry	KOAc (eq.)	EtOH (μL)	yield (%)	dr	ee%
1	2.0	1.0 (eq.)	22	>20:1	93
2	2.0	5.0 (eq.)	41	>20:1	93
3	2.0	100	57	>20:1	93
4	2.0	200	57	>20:1	93
5	0.2	100	11	>20:1	70
6	1.0	100	39	>20:1	89
7	5.0	100	62	>20:1	93
8	**10.0**	**100**	**66**	**>20:1**	**93**

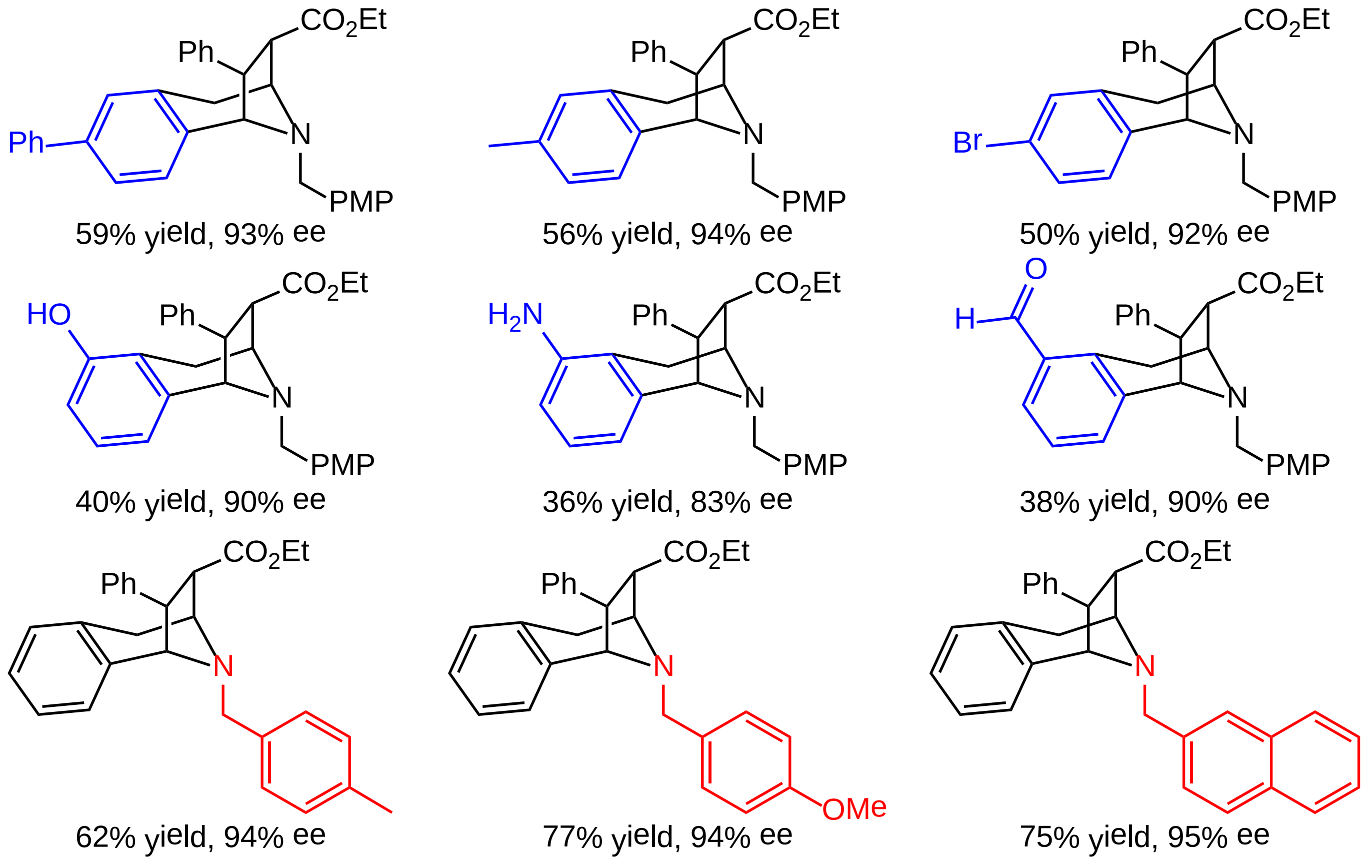
Substrate Scope



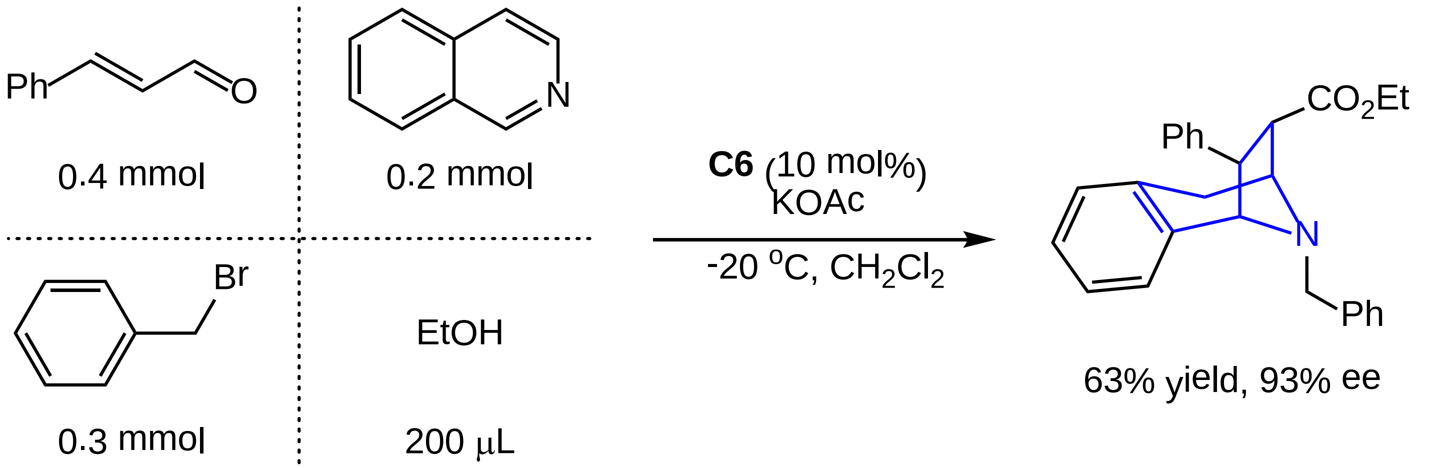
entry	Ar	yield (%)	dr	ee %
1	C_6H_5	66	>20:1	93
2	4-MeC_6H_4	70	>20:1	96
3	4-MeOC_6H_4	64	>20:1	96
4	2-MeOC_6H_4	65	>20:1	91
5	4-$Me_2NC_6H_4$	64	>20:1	>99
6	4-$N_3C_6H_4$	62	>20:1	84
7	4-FC_6H_4	50	>20:1	84
8	2-Furyl	50	>20:1	96

Substrate Scope

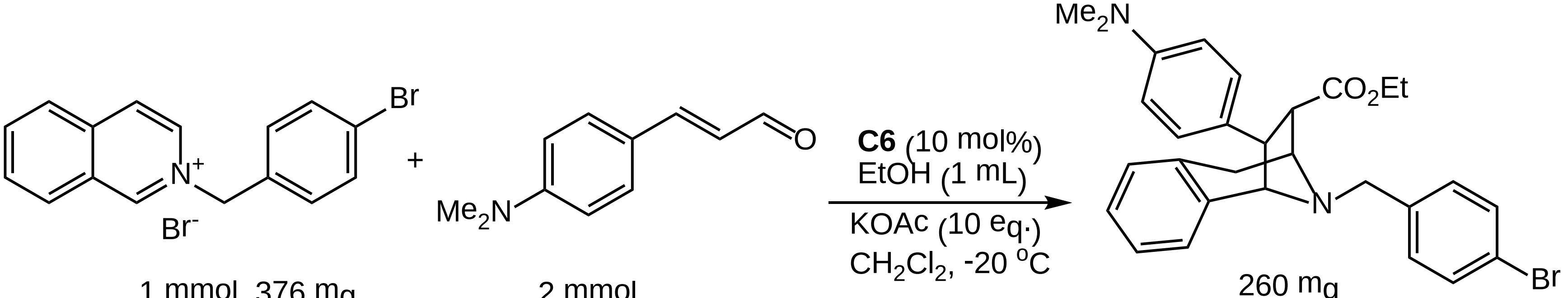




Multicomponent reaction



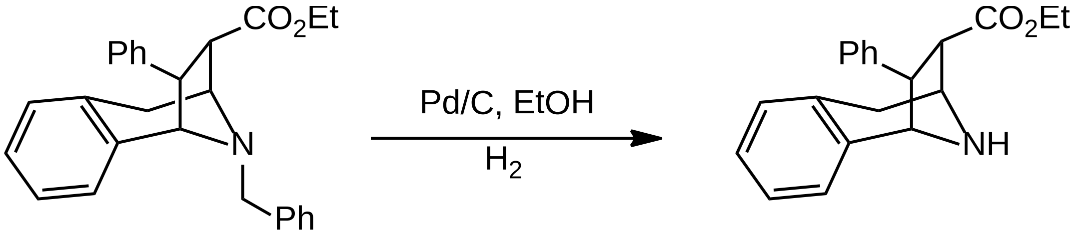
Further transformation



1 mmol, 376 mg

2 mmol

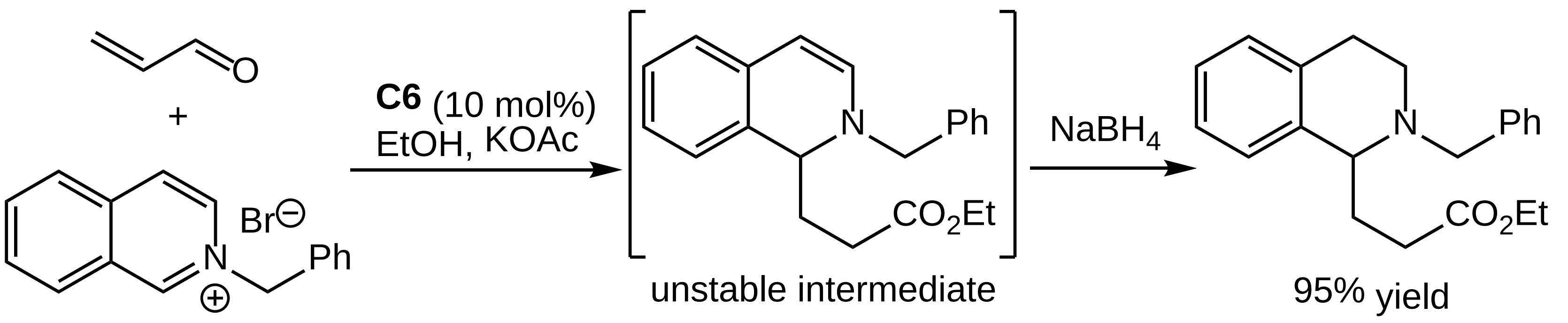
260 mg
50%, 99.5% ee



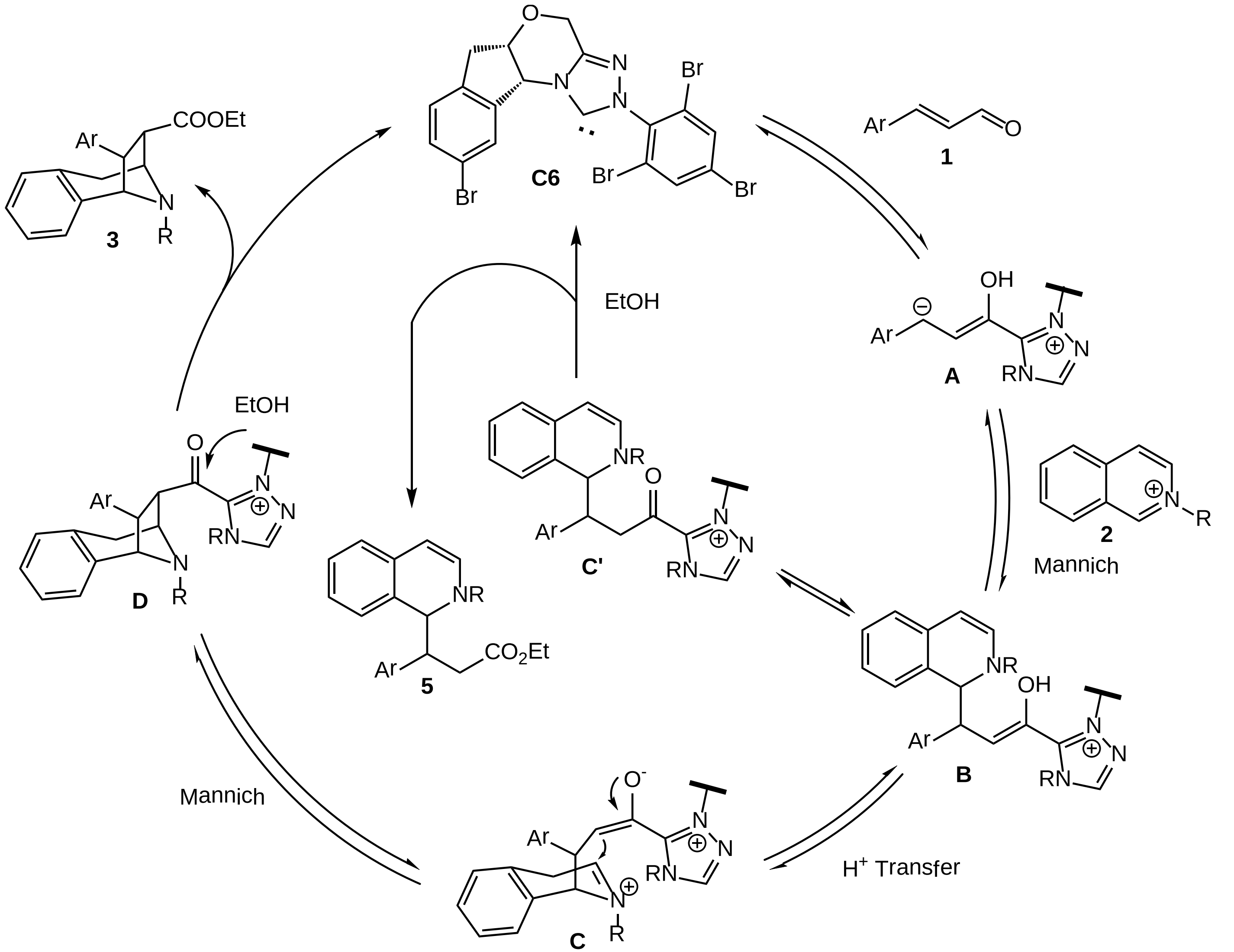
93% ee

72% yield, 93% ee

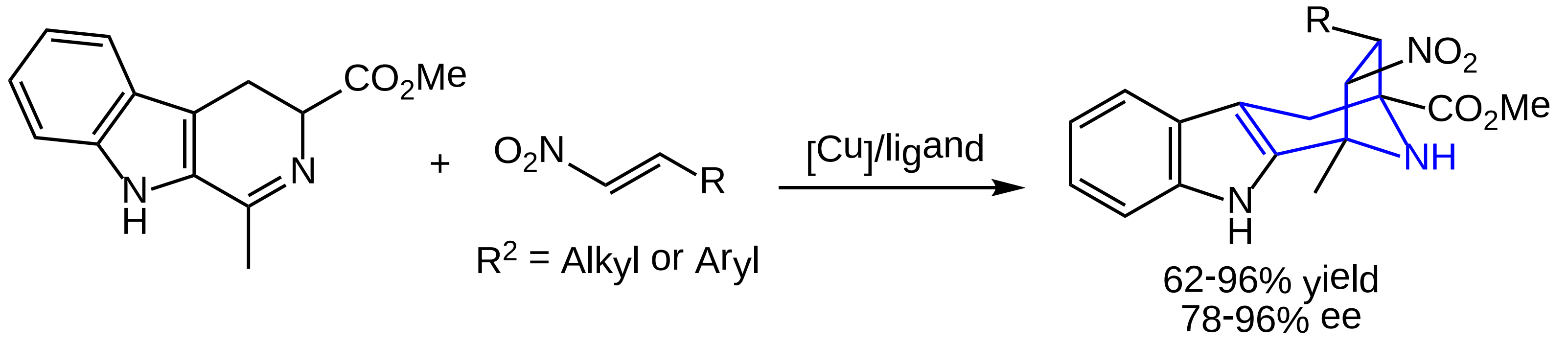
Mechanism study



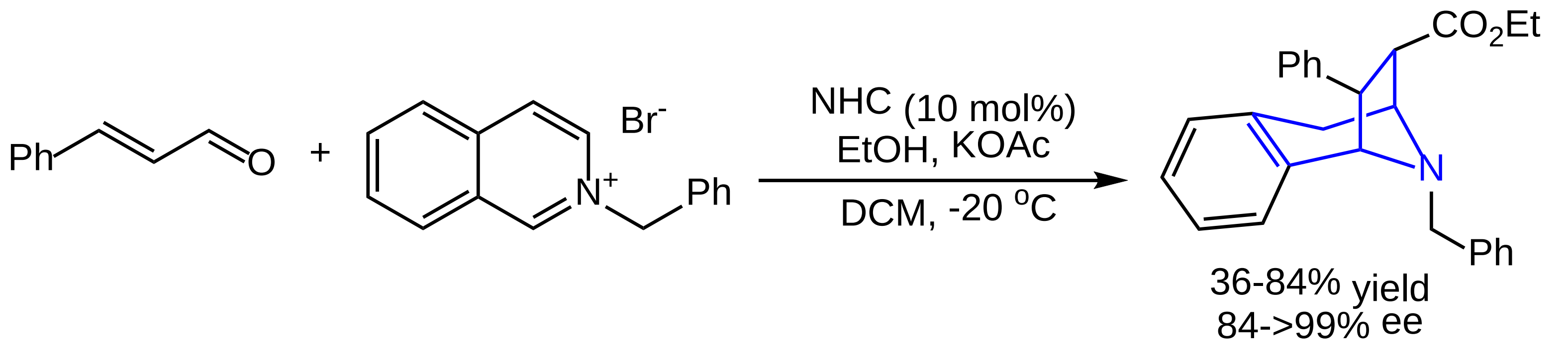
Proposed mechanism



Summary



Waldmann, H. *et al*. *Angew. Chem. Int. Ed*. **2013**, *52*, 12892.



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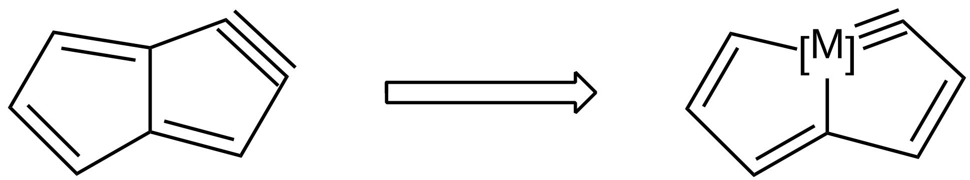
The first paragraph

The tropane (8-azabicyclo[3.2.1]octane) skeleton is widespread in both natural products and synthetic compounds with a wide range of biological activity. Many tropane derivatives play a key role in a large number of neurological and psychiatric diseases, such as Parkinsons disease, depression, and panic disorder. Maraviroc, with a tropane structural core, has been used in the treatment of HIV infection and deserves considerable attention. Benzotropane, containing a phenyl ring in the tropane moiety, also occurs in numerous lead compounds and pharmaceuticals for the treatment of type 2 diabetes and antitumor drug candidates. The medicinal relevance of tropane derivatives has stimulated considerable interest among synthetic chemists, and several catalytic methods have been developed for the construction of optically pure tropane frameworks.

The last paragraph

In summary, we have successfully developed the first chiral-NHC-catalyzed asymmetric dearomatizing double Mannich reaction of isoquinolines to enable the straightforward and efficient synthesis of biologically important tropanes bearing four contiguous stereogenic centers with high levels of diastereo- and enantioselectivity. A unique feature of this strategy is the use of readily available isoquinolines to provide two reactive sites for dearomatization reactions. This highly convergent and functional-group-tolerant strategy enables the rapid construction of complex compounds from simple, readily available starting materials.

碳龙化学：全新的芳香性分子骨架基元



M = Os, Ru, Rh, Ir

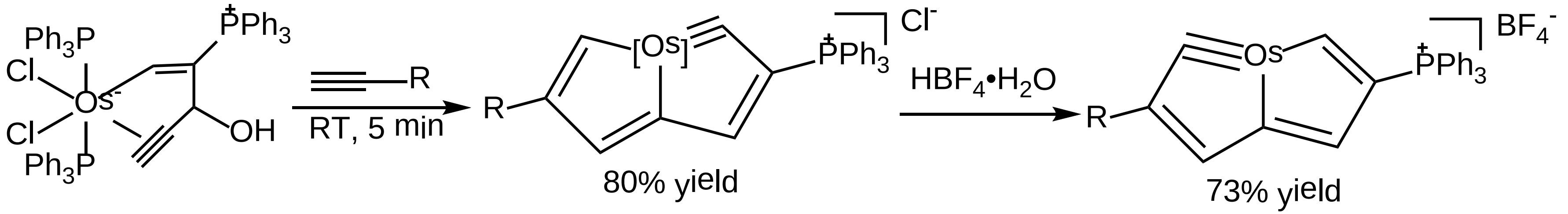
戊搭炔
反芳香性

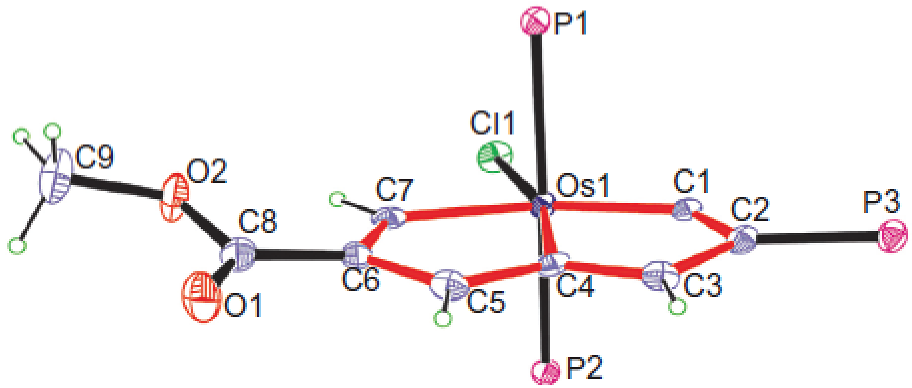
金属杂戊搭炔
芳香性

卡拜碳键角129.5 º

Xia, H. *et al. Nat. Chem.* **2013**, *5*, 698.

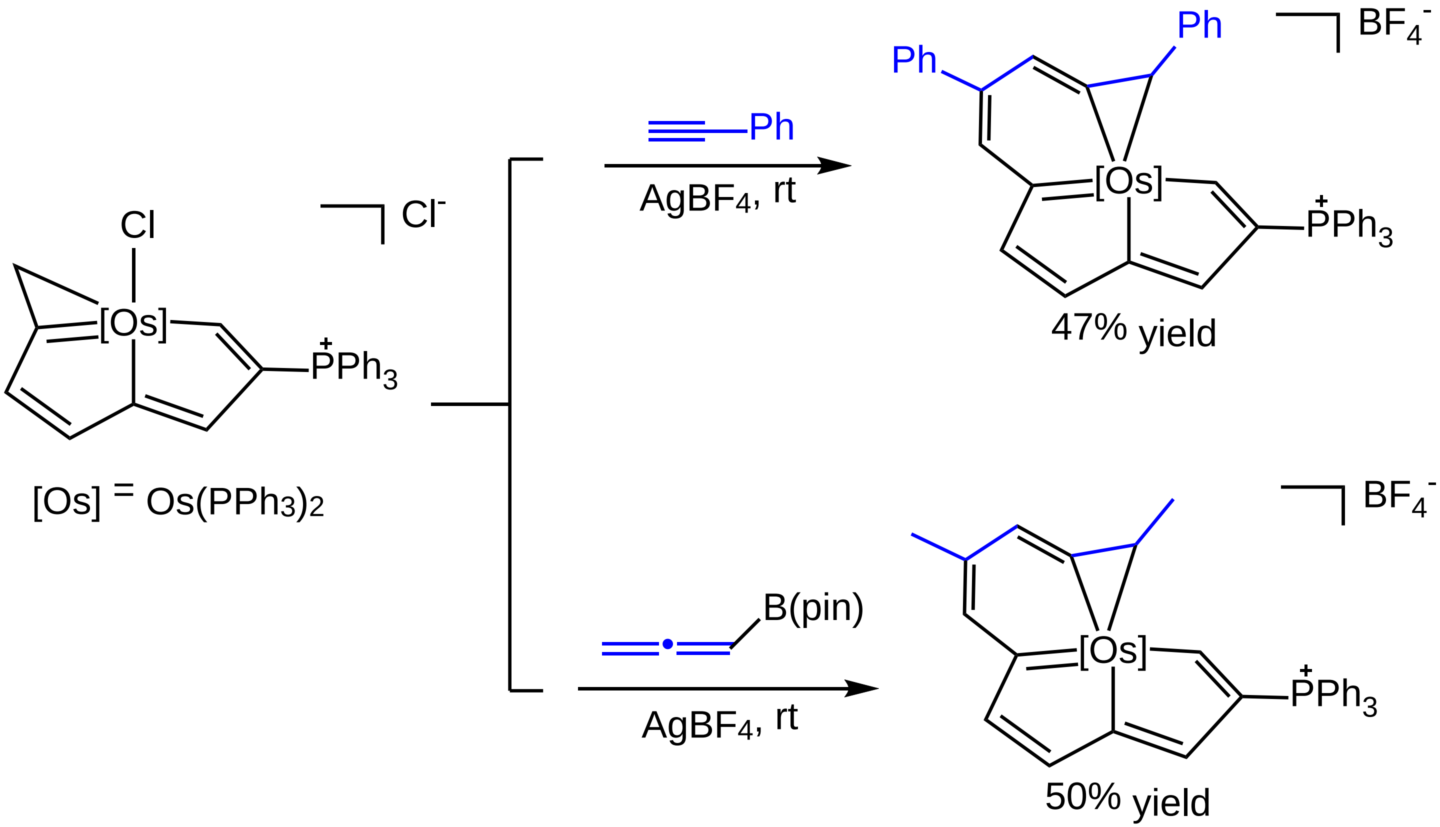
碳龙化学：





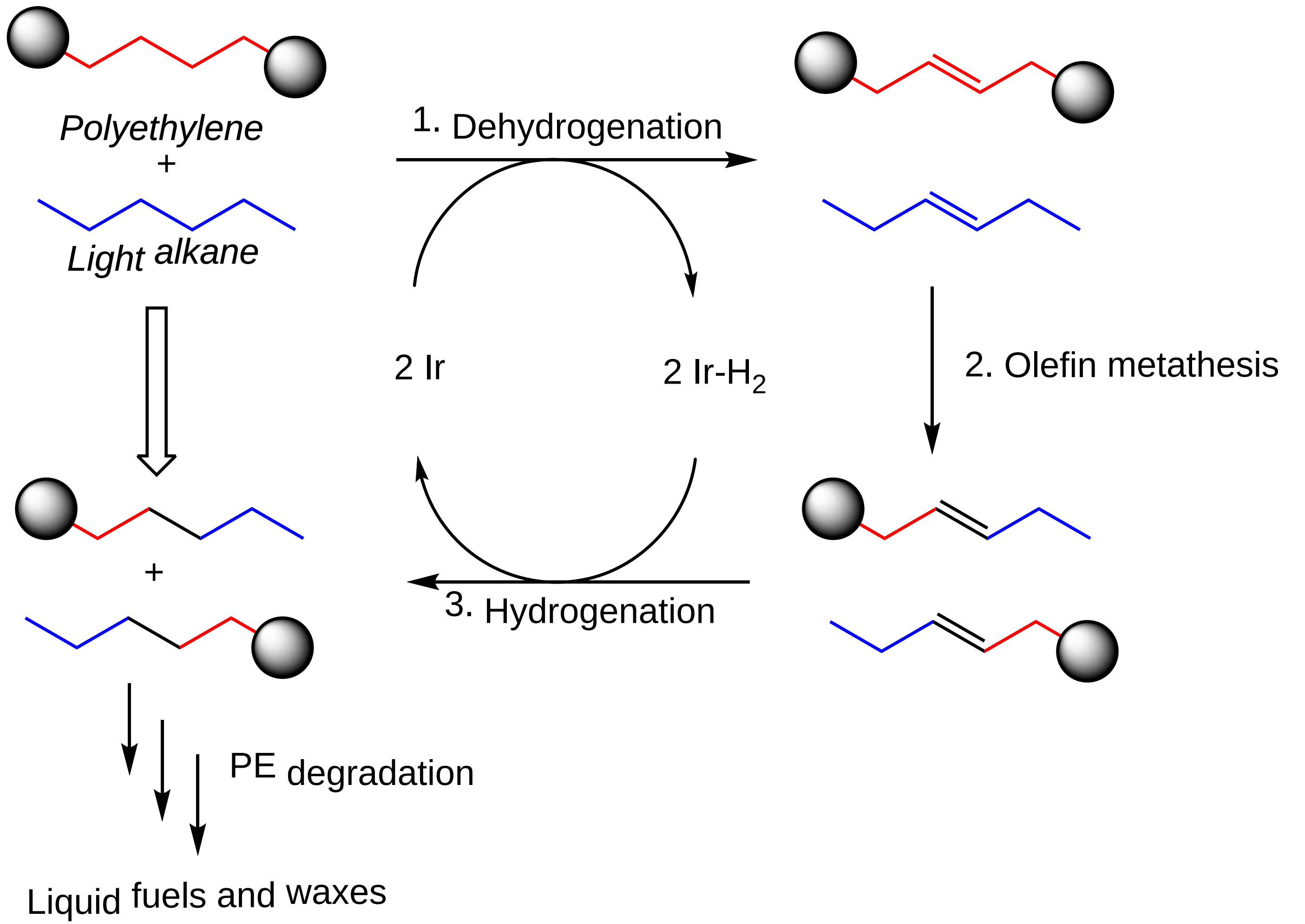
Xia, H. *et al. Nat. Chem.* **2013**, *5*, 698.

碳链增长



Xia, H. *et al. Sci. Adv.* **2016**; 2:e1601031.

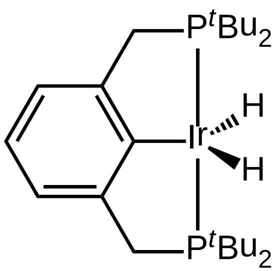
烷烃交叉复分解



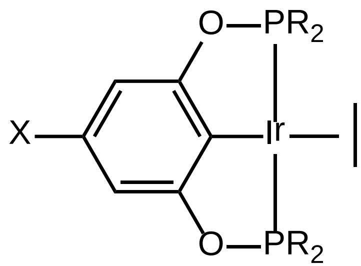
Huang, Z. *et al*. *Sci. Adv.* **2016**; 2:e1501591.

烷烃交叉复分解

Dehydrogenation and hydrogenation catalysts:



1



2: R = *t*-Bu, X = *t*-Bu$_2$PO
3: R = *i*-Pr, X = OMe

Olefin metathesis catalyst:

Re_2O_7/Al_2O_3

0.3 g each

8 mL petroleum ether

2/γ-Al_2O_3 and Re_2O_7/γ-Al_2O_3

0.3 g each	Isolated oil (C_7-C_{38})	Wax
HDPE plastic bottle	1.8 g	2 mg
Food packaging film	0.77 g	7 mg
Grocery shopping bag	0.77 g	3 mg