Literature Report

Aldehydes as alkyl carbanion equivalents for additions to carbonyl compounds

Reporter: Chang-Bin Yu

Checker: Hong-Qiang Shen

2017-09-04

H. Wang, I.-J. Dai, **C.-J. Li**, *Nat. Chem.* **2017**, *9,* 374.

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- Introduction
- Catalytic asymmetric umpolung reactions of imines
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CV of Chao-Jun Li

Prof. Chao-Jun Li

1983年在郑州大学获学士学位

1988年在北京化学所获得硕士学位

1992年在加拿大麦吉尔大学获得博士学位

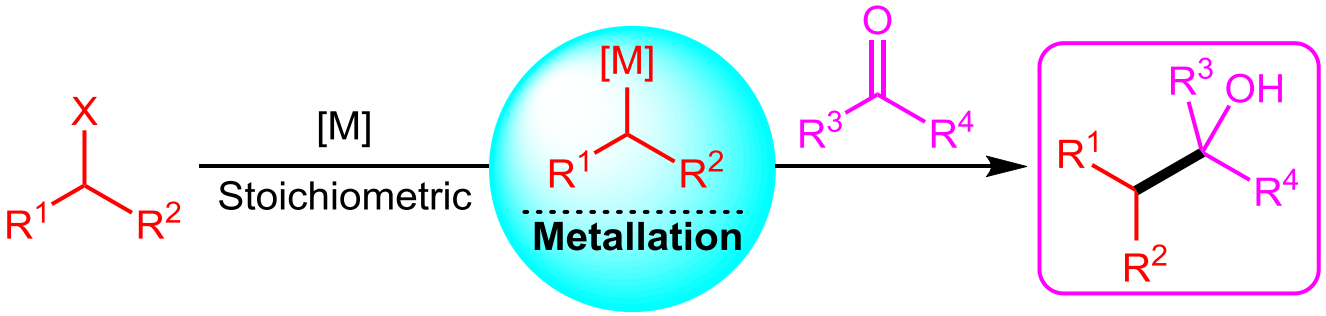
1992至**1994**年在美国斯坦福大学**Barry M. Trost**教授小组 博士后研究

1994年任美国杜兰大学助理教授、**1998**年任副教授、**2000**年起任教授

2003年起任麦吉尔大学教授、加拿大绿色化学首席科学家

2009年起任麦吉尔大学**E. B. Eddy** 讲座教授

Generation of carbanions



R^1, R^2, R^3, R^4 = alkyl, aryl or H

X = Cl, Br, I, etc.

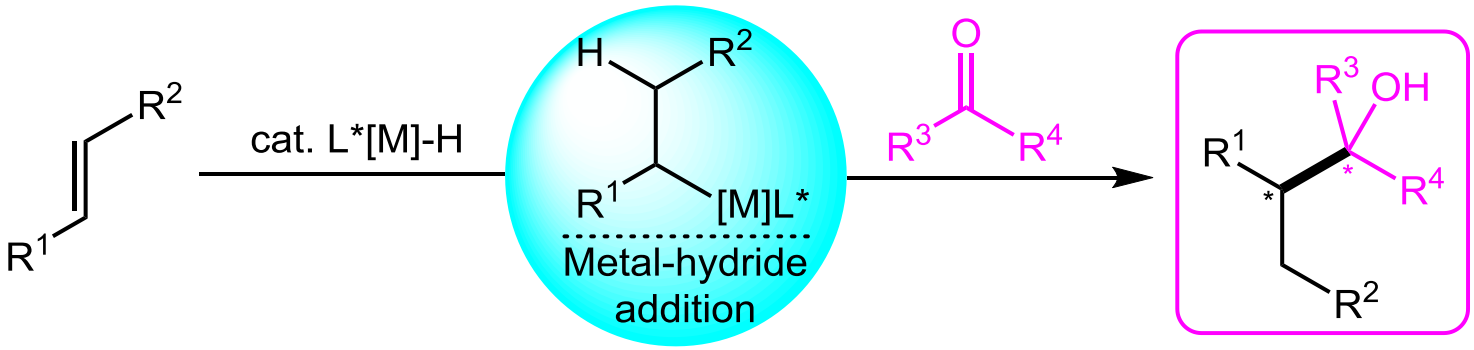
[M] = Mg, Li, Cu, Zn, Ti, etc.

缺点：

1）当量的金属和卤代物，反应后产生大量的金属废弃物;

2）金属试剂活泼，官能团兼容性差。

Generation of carbanions

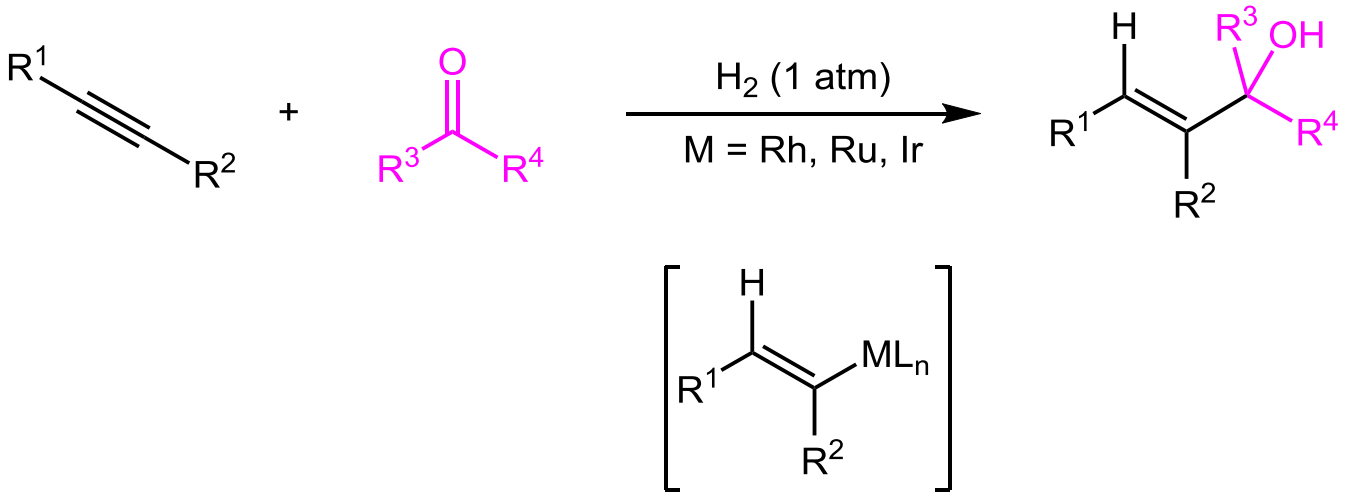


R^1, R^2, R^3, R^4 = alkyl, aryl or H

[M] = Ir, Rh, Ru, Cu, Ni, etc.

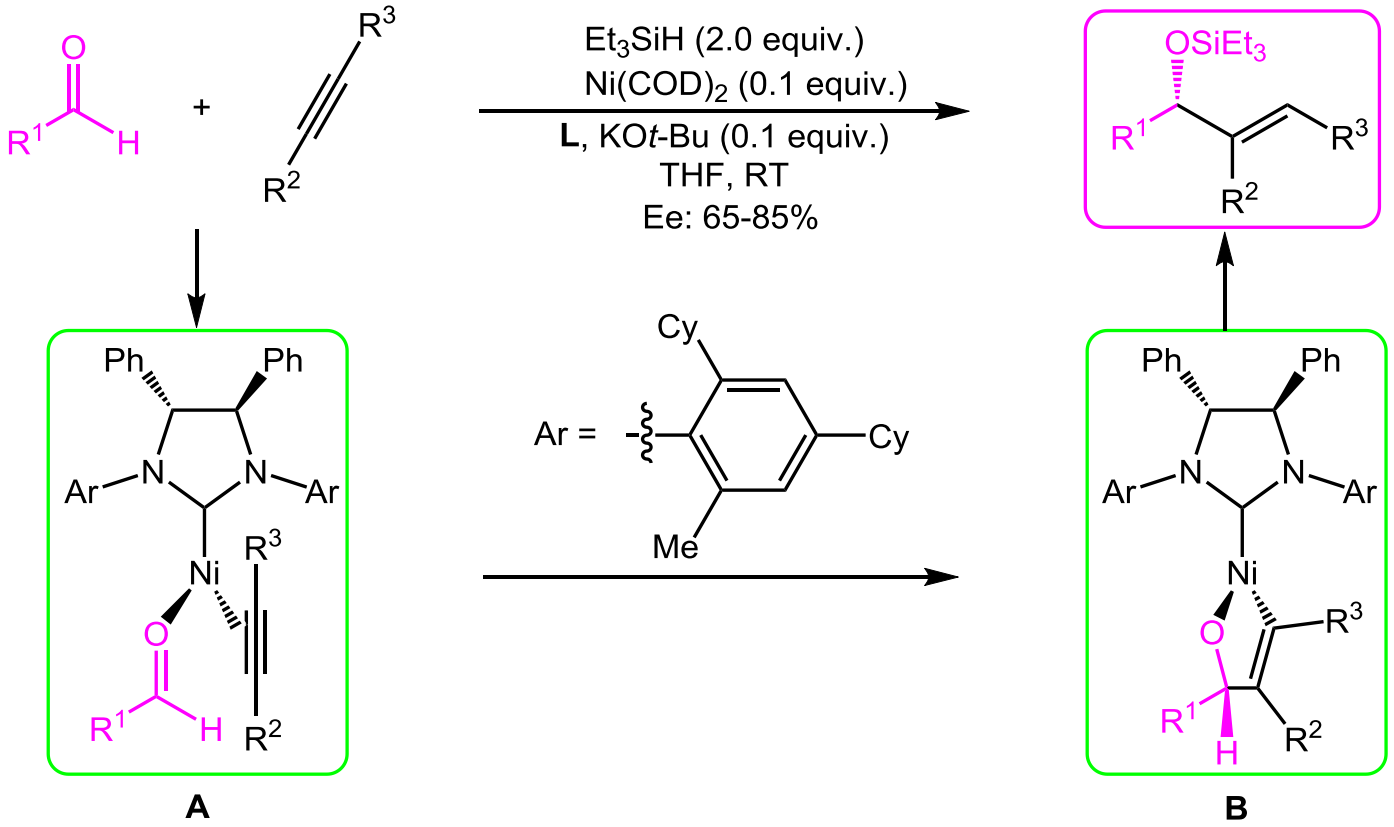
Krische, Hoveyda, Montgomery, Jamison, Buchwald, Liu, etc.

Hydrogenation intermediates



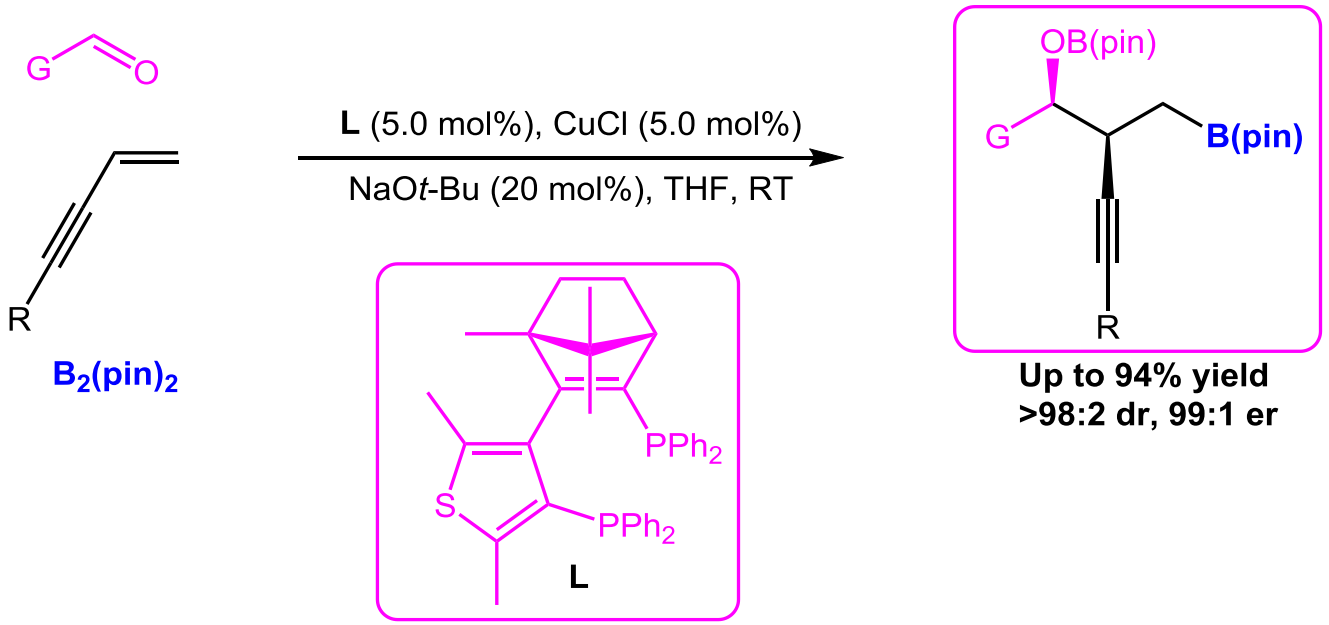
M. J. Krische, et al. *Acc. Chem. Res*. **2004**, *37*, 653; *Acc. Chem. Res*. **2007**, *40*, 1394.

Nickel-catalyzed aldehyde/alkyne reductive couplings



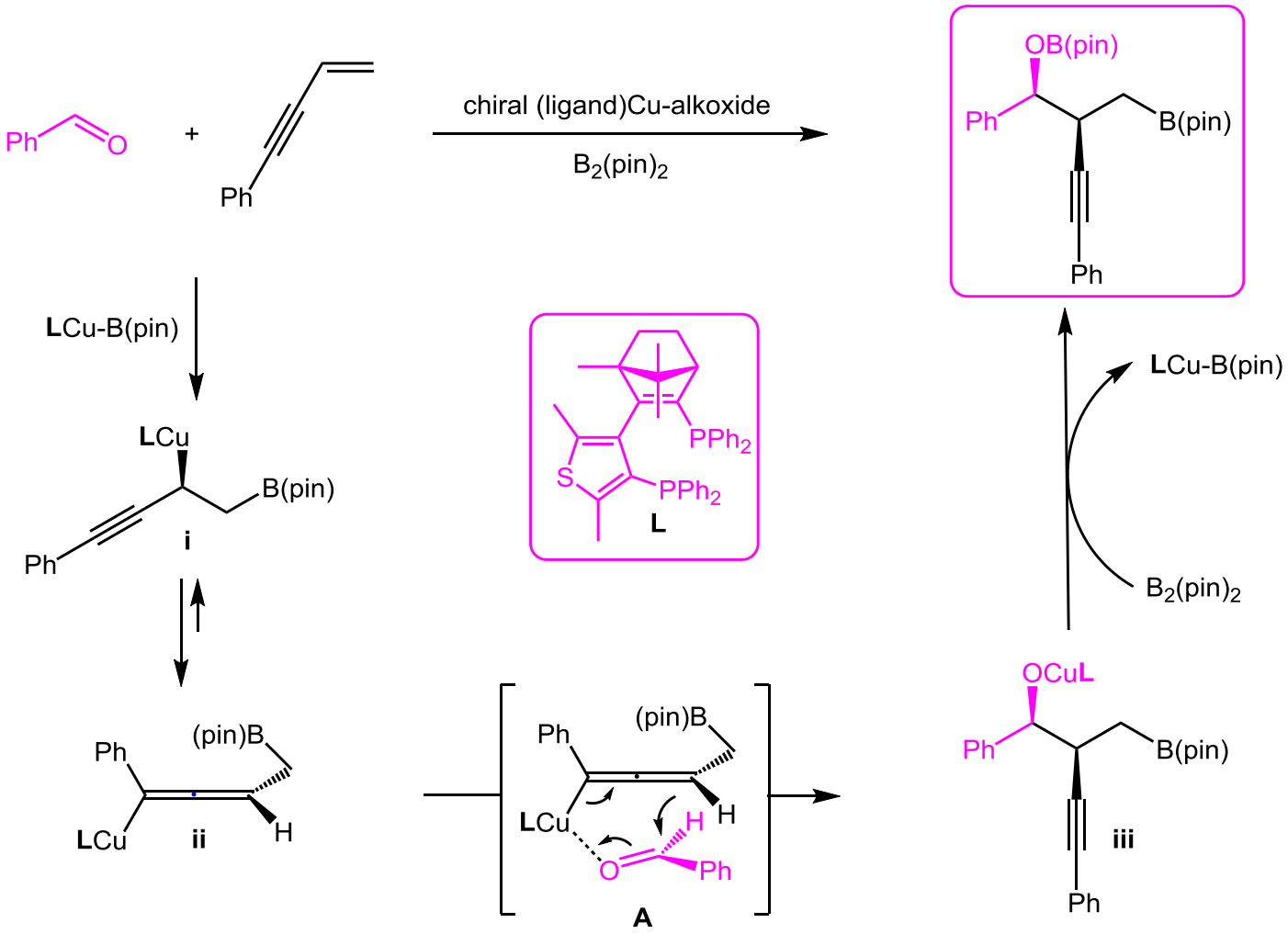
J. Montgomery, et al. *J. Am. Chem. Soc.* **2007**, *129*, 9568.

Copper-catalyzed reaction of aldehyde/1,3-enyne/boron



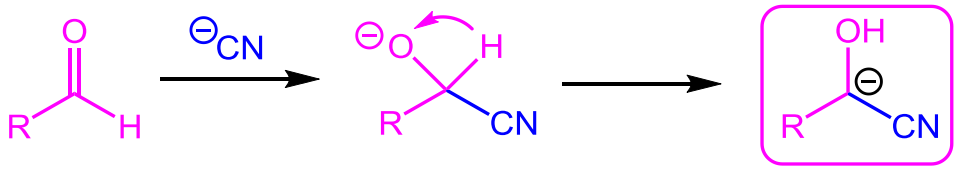
A. H. Hoveyda, et al. *J. Am. Chem. Soc*. **2014**, *136*, 11304.

Possible pathway

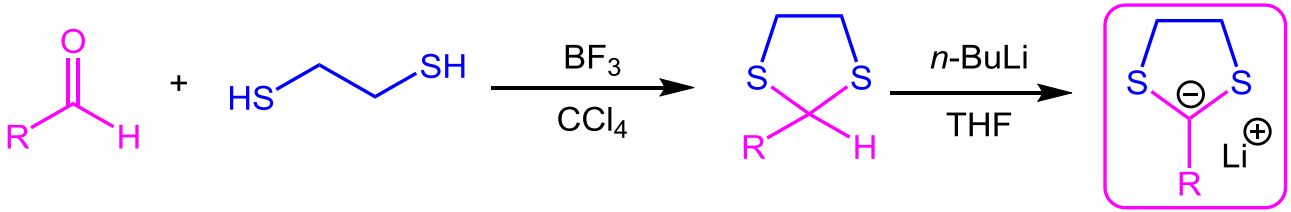


Umpolung reactions of aldehydes

Benzoin condensation

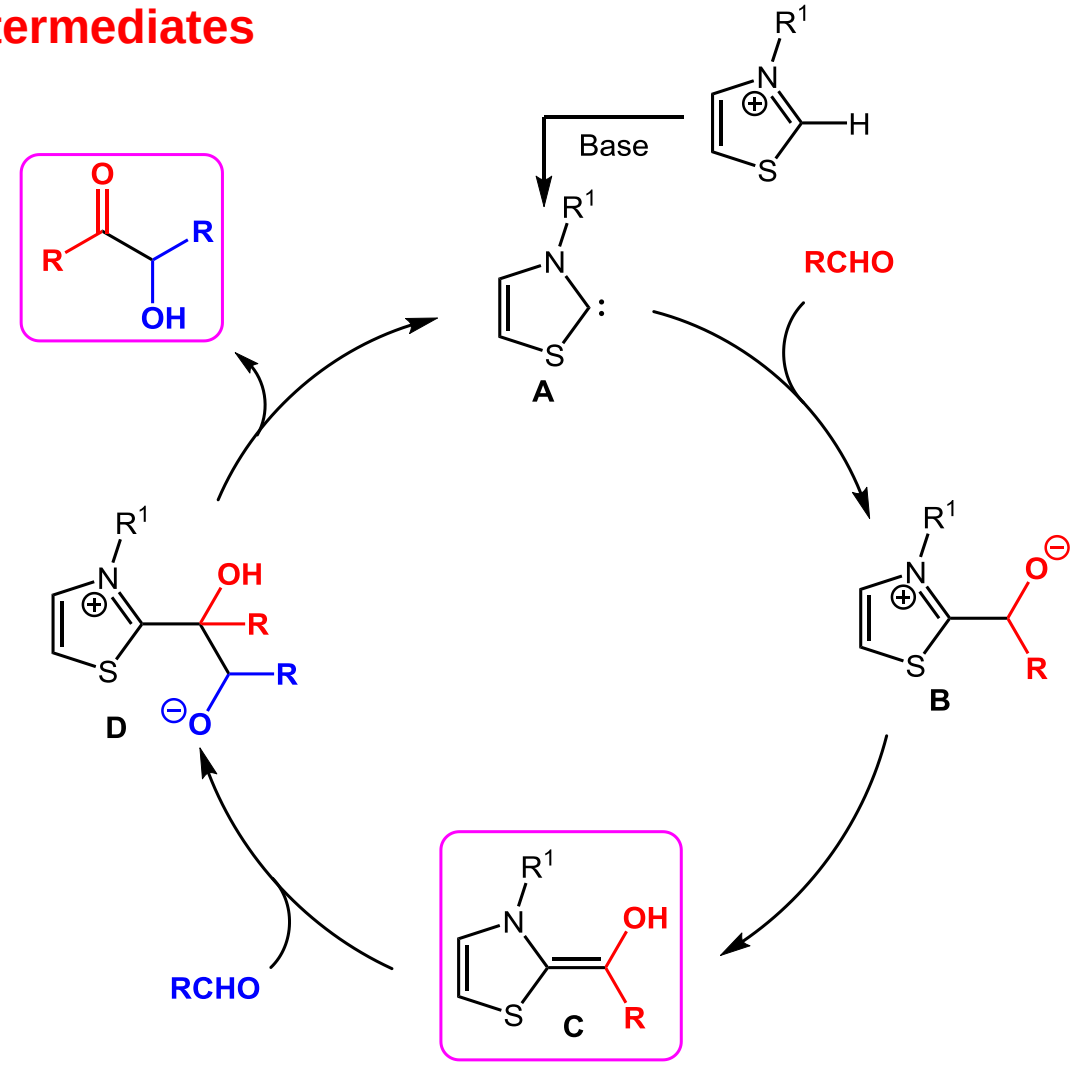


Thioketal intermediates

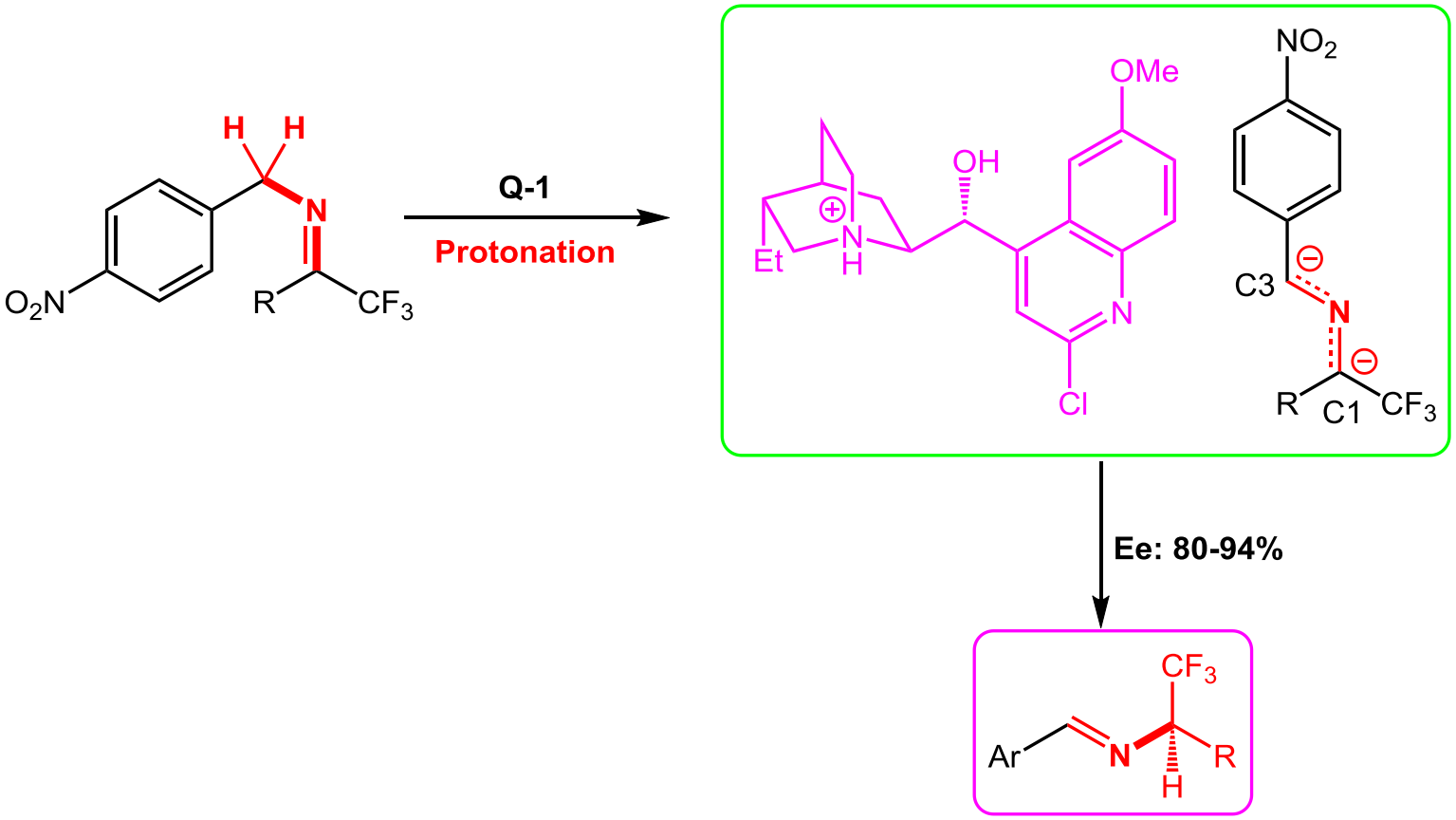


Umpolung reactions of aldehydes

Carbene intermediates

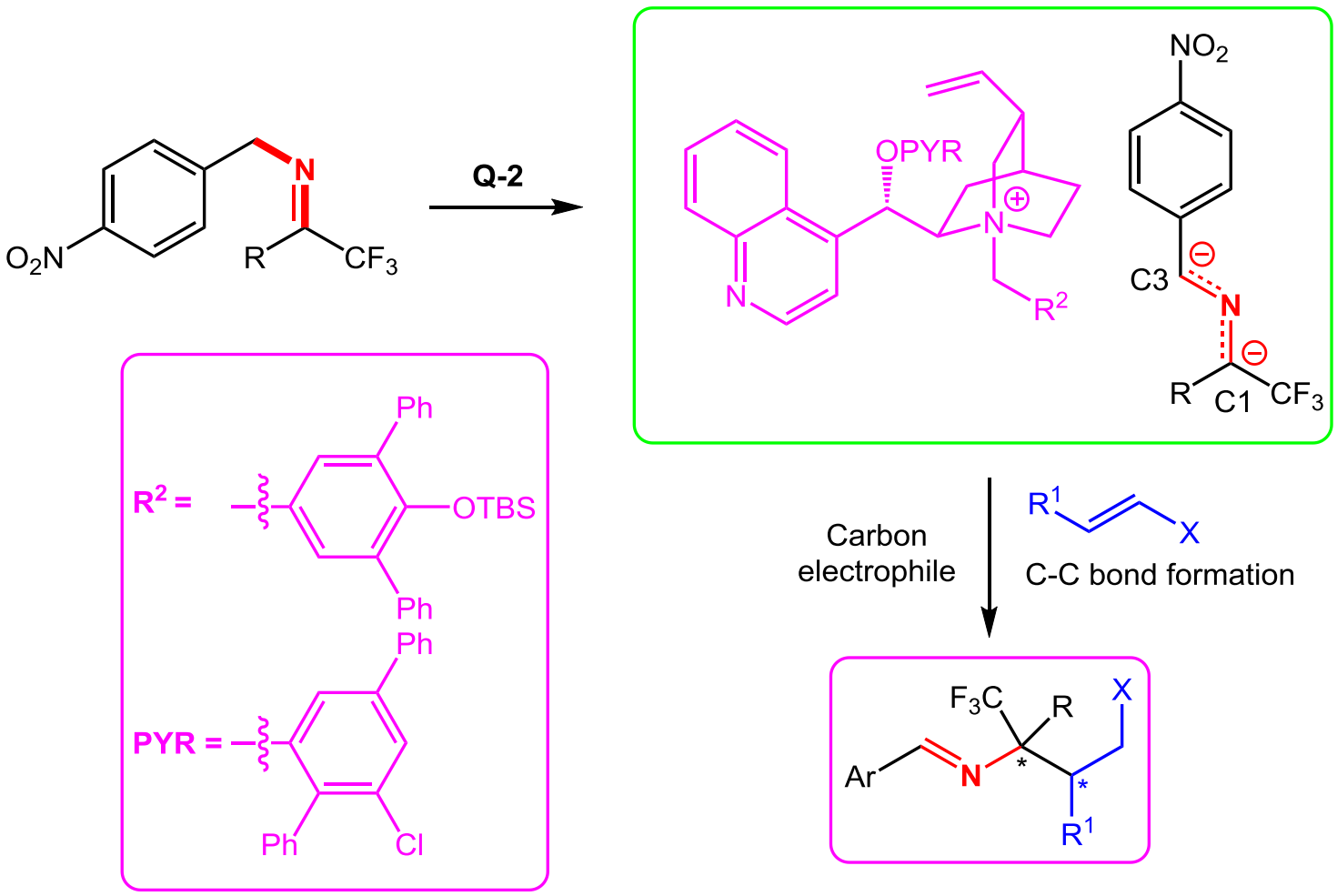


Umpolung reactions of imines



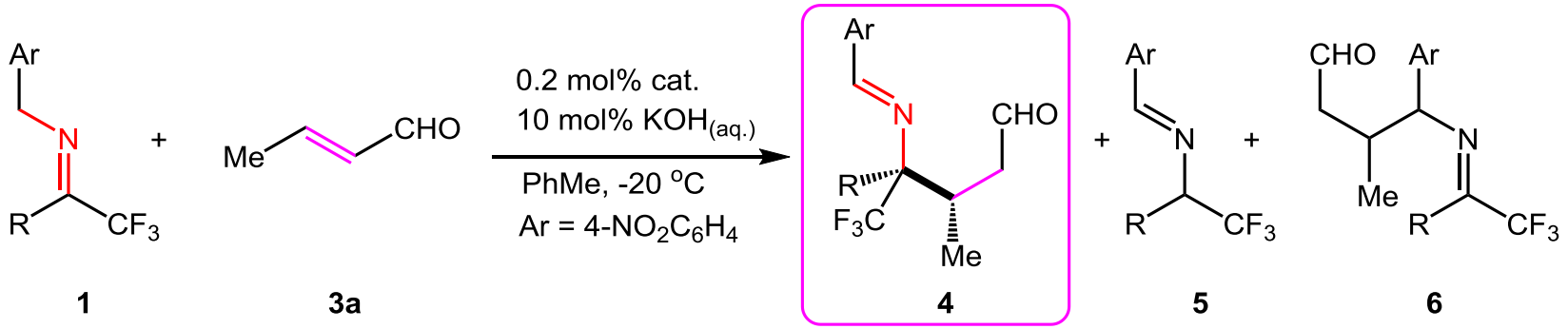
L. Deng, et al. *J. Am. Chem. Soc.* **2012**, *134*, 14334.

Umpolung reactions of imines



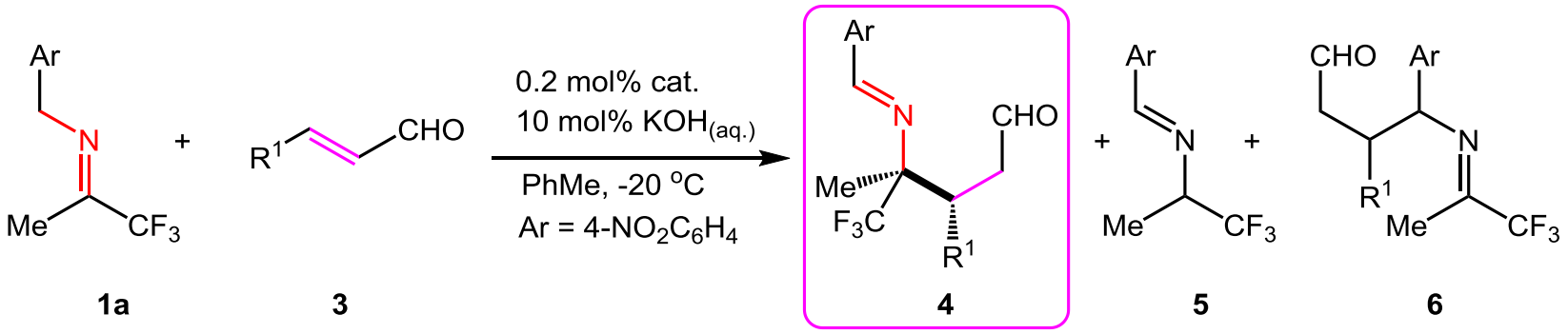
Y.-W. Wu, L. Hu, Z. Li, **L. Deng**, *Nature* **2015**, *523*, 445.

Substrate scope



Entry	R	t (h); Conv. (%)	**4:5**; **4:6**	d.r. of **4**	Yield (%)	Ee (%)
1	Me	5; 99	>95:5; >95:5	93:7	81	95
2	Et	5; 97	>95:5; >95:5	91:9	84	94
3	*n*-Bu	5; 98	>95:5; >95:5	91:9	83	96
4	$Br(CH_2)_4$	5; 99	>95:5; >95:5	91:9	75	96
5	$BnO(CH_2)_3$	7; 94	>95:5; >95:5	91:9	72	96
6	$CyCH_2$	12; 98	91:9; >95:5	93:7	54	95

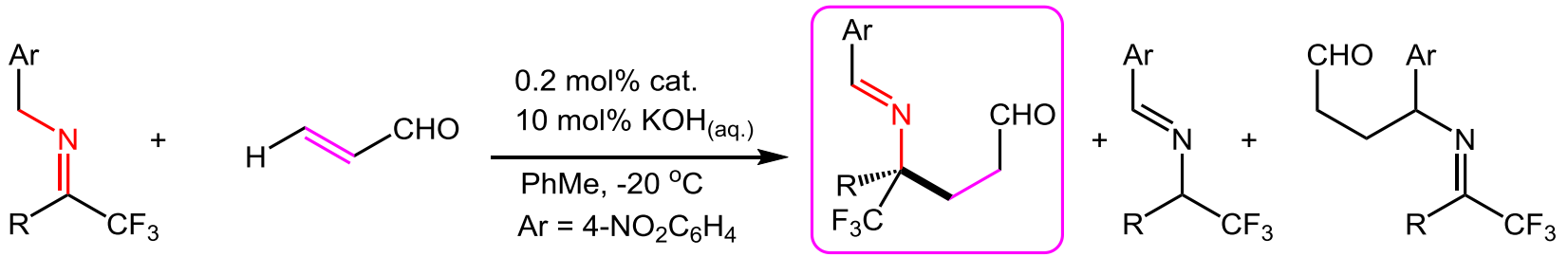
Substrate scope



1a **3** **4** **5** **6**

Entry	R^1	t (h); Conv. (%)	**4:5**; **4:6**	d.r. of **4**	Yield (%)	Ee (%)
1	CH_3CH_2	5; 99	89:11; >95:5	>95:5	64	95
2	$CH_3(CH_2)_5$	12; 93	86:14; >95:5	>95:5	51	96
3	Ph	12; 98	>95:5; 68:32	>95:5	51	91

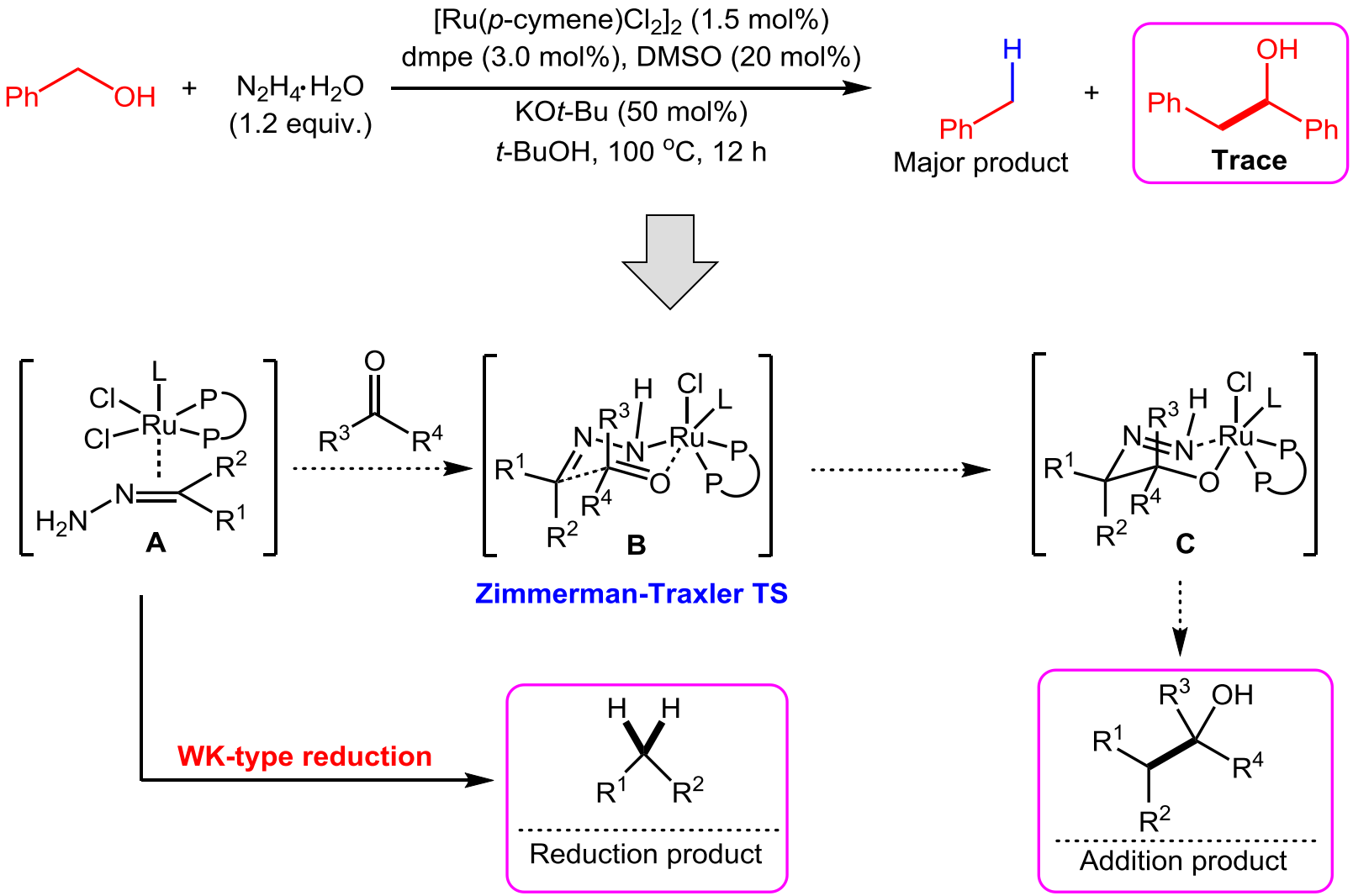
Substrate scope



1 **3e** **4** **5** **6**

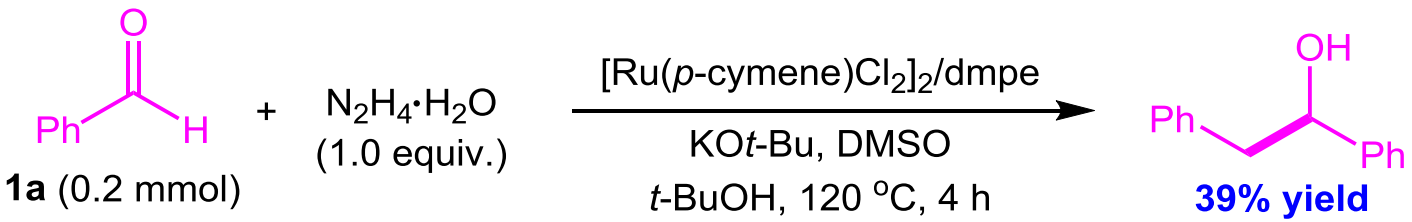
Entry	R	t (h); Conv. (%)	**4:5**; **4:6**	Yield (%)	Ee (%)
1	CH_3	3; 99	>95:5; >95:5	89	92
2	CH_3CH_2	3; 99	>95:5; >95:5	82	91
3	$Br(CH_2)_4$	3; 97	>95:5; >95:5	84	91
4	$CyCH_2$	3; 99	>95:5; >95:5	90	92
5	Ph	3; 99	94:6; >95:5	71	94
6	*p*-$MeOC_6H_4$	3; 94	92:8; >95:5	67	94
7	*p*-$CF_3C_6H_4$	3; 99	88:12; >95:5	78	92
8	PhCH=CH	1; 99	>95:5; >95:5	90	93

Mechanistic hypothesis



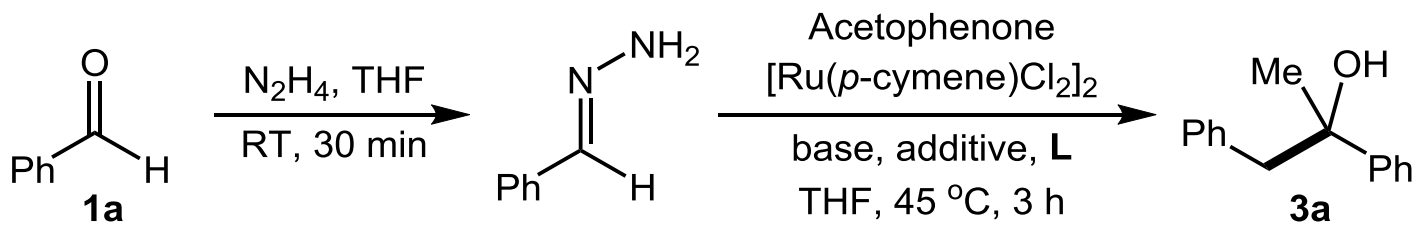
C.-J. Li, et al. *J. Am. Chem. Soc*. **2016**, *138*, 5433; *Nat. Chem.* **2017**, *9*, 374.

Preliminary result



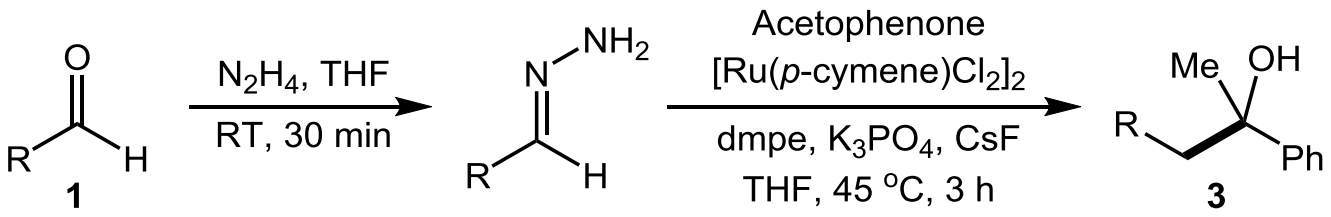
C.-J. Li, et al. *Nat. Chem.* **2017**, *9*, 374.

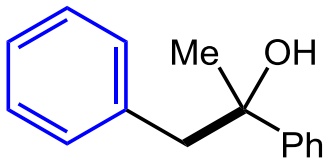
Evaluation of reaction parameters



Entry	Ligand	Base	Additive	**3a** (%)
1	-	K_3PO_4	CsF	13
2	dppe	K_3PO_4	CsF	78
3	dppp	K_3PO_4	CsF	92
4	dppf	K_3PO_4	CsF	58
5	dmpe	-	CsF	3
6	dmpe	K_2CO_3	CsF	57
7	dmpe	Cs_2CO_3	CsF	51
8	dmpe	KO*t*-Bu	CsF	82
9	**dmpe**	**K_3PO_4**	**CsF**	**95**
10	dmpe	K_3PO_4	-	85

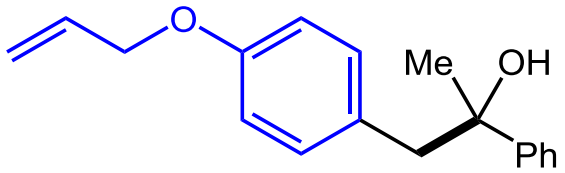
Substrate scope



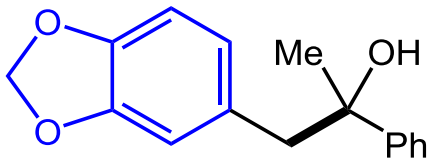


3a, 94%

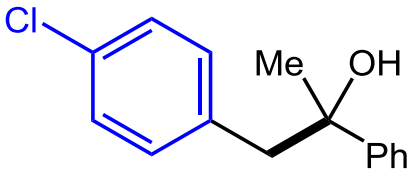
3b, 58%



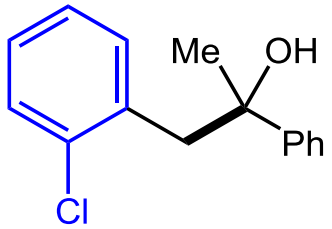
3c, 98%



3d, 86%

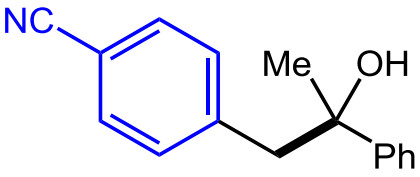


3e, 85%

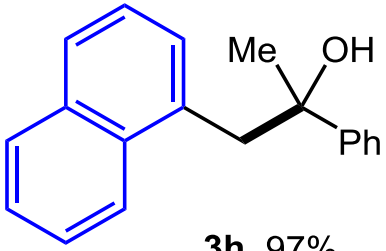


3f, 65%

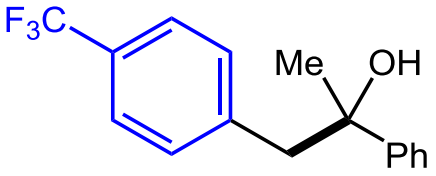
Substrate scope



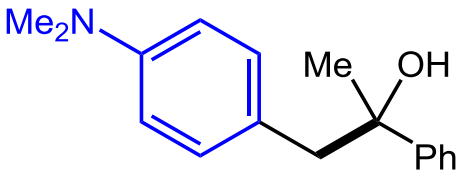
3g, 43%



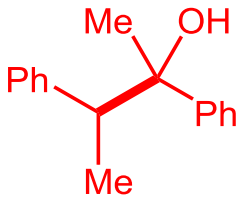
3h, 97%



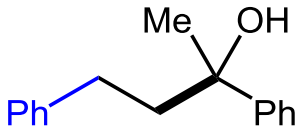
3i, 95%



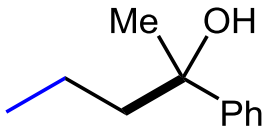
3j, 67%



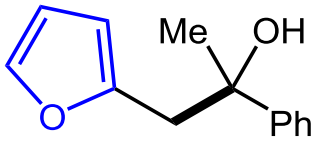
3k, 30%



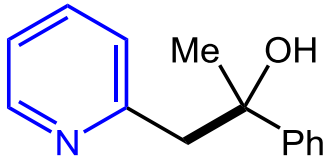
3l, 23%



3m, 20%

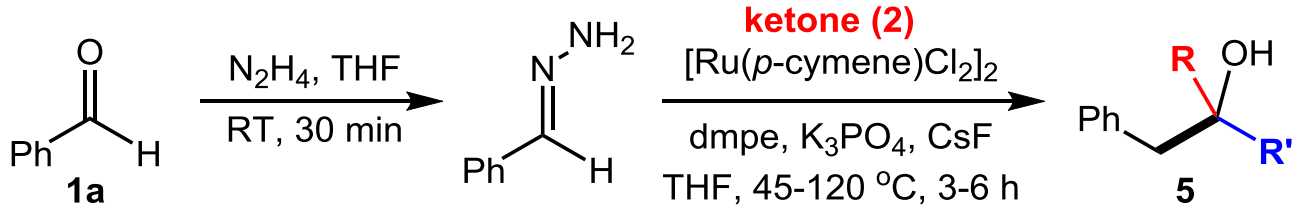


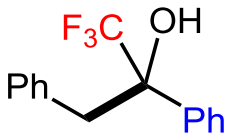
3n, 75%



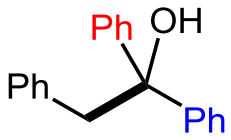
3o, 53%

Substrate scope

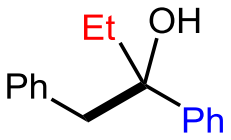




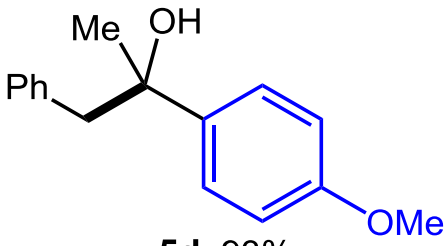
5a, 89%



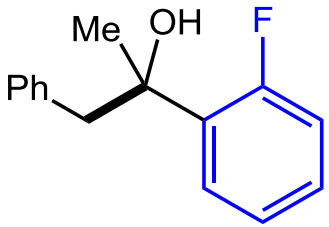
5b, 65%



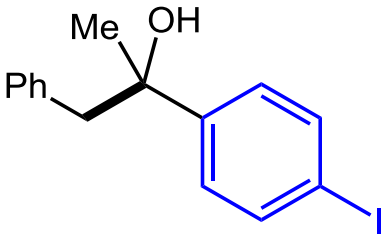
5c, 93%



5d, 93%

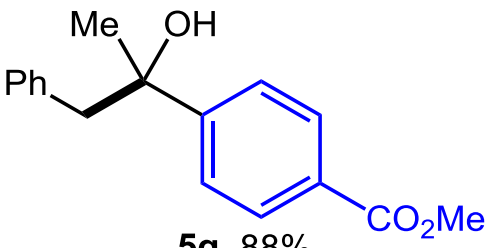


5e, 84%

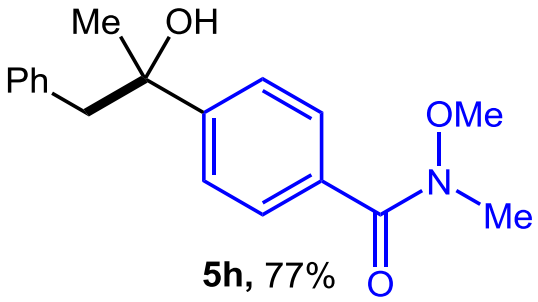


5f, 79%

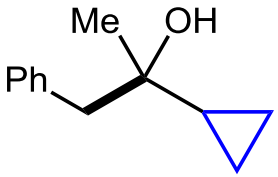
Substrate scope



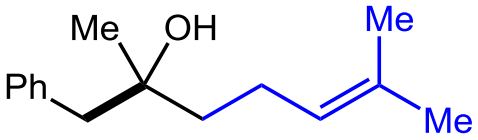
5g, 88%



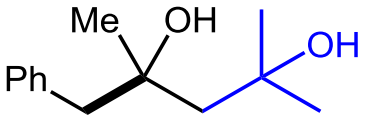
5h, 77%



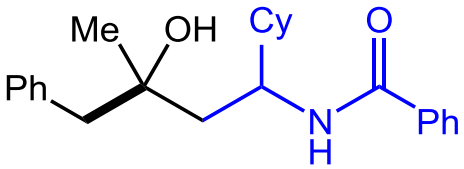
5i, 85%



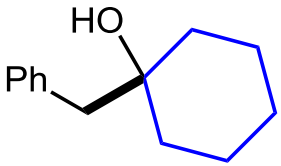
5j, 71%



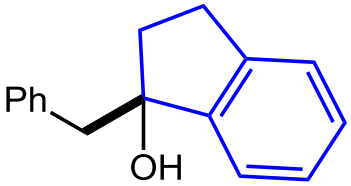
5k, 50%



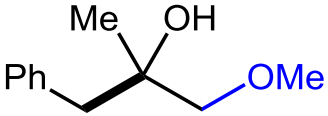
5l, 85%



5m, 88%

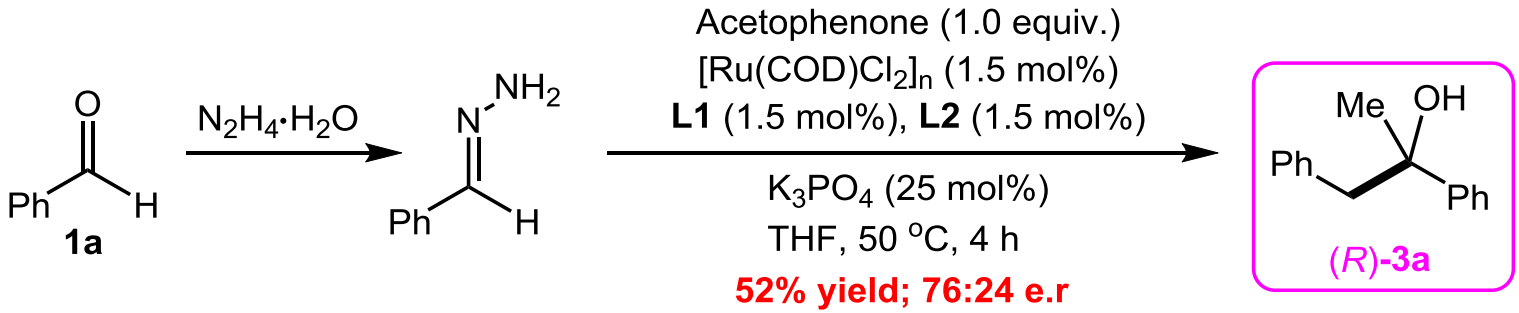


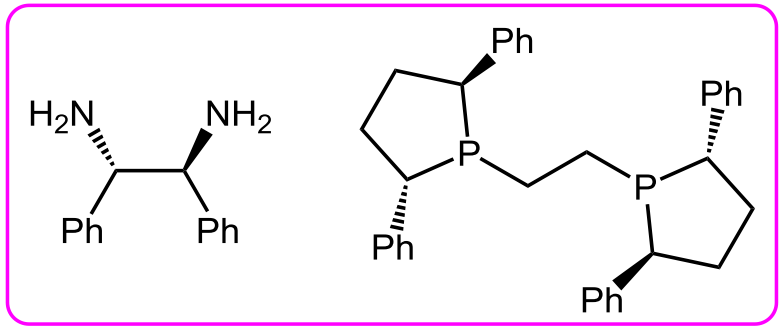
5n, 70%



5o, 55%

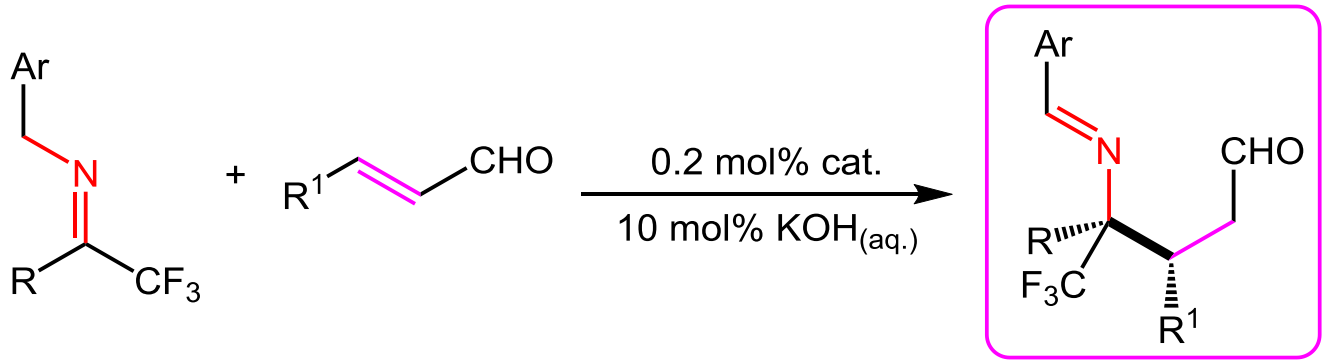
Enantioselective carbonyl addition





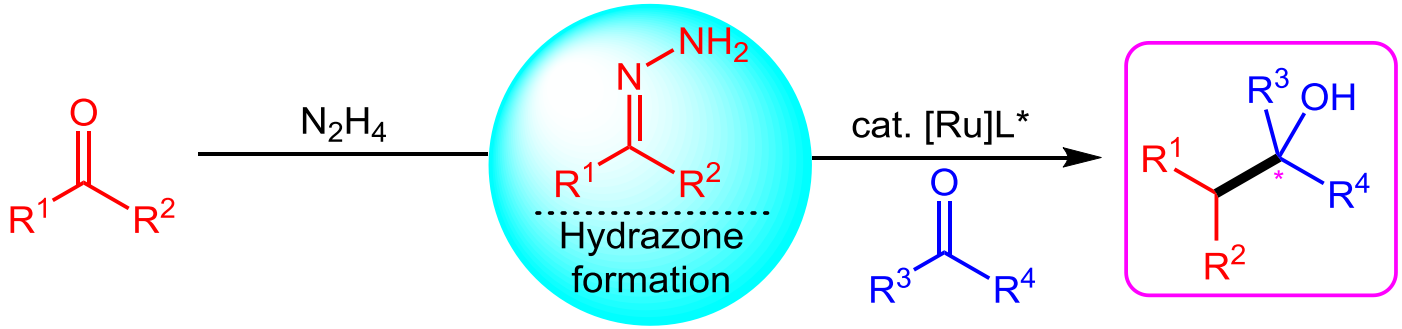
Summary

Umpolung reactions of imines:



Y.-W. Wu, L. Hu, Z. Li, **L. Deng**, *Nature* **2015**, *523*, 4451.

Umpolung reactions of aldehydes:



H. Wang, I.-J. Dai, **C.-J. Li**, *Nat. Chem.* **2017**, *9*, 374.

The first paragraph:

The nucleophilic addition of organometallic reagents to carbonyl compounds is a fundamental process in organic synthesis. This simple alkylation process provides a reliable method for generating a wide array of alcohol products. The discovery of Grignard reagents as carbanion equivalents and their subsequent additions to carbonyl compounds marked a milestone in synthetic chemistry. Since then, other organometallic reagents, such as those based on zinc, aluminium, copper and titanium, have been sought and used to achieve better selectivity. However, the preparation of these organometallic reagents requires stoichiometric quantities of metal.

The last paragraph:

In summary, we have described a catalytic umpolung strategy to use aldehydes as alkyl carbanion equivalents for additions to carbonyl compounds. The full potential of this novel chemistry is yet to be revealed, as it is currently limited by accessible nucleophilic carbonyls, and safety and toxicity issues concerning hydrazine. We believe that this chemistry is a stepping stone towards carbon–carbon bond forming processes built upon more sustainable chemical feedstocks. With a deeper understanding of this reaction, new strategies using carbonyl-derived carbanion equivalents for chemical bond formation beyond carbon–carbon bonds are likely to emerge.

Wolff–Kishner (WK) reduction