UMR 8123-CNRS-UCP-ESCOM

Synthèse Organique Sélective et Chimie Organométallique

Iron and Cobalt-catalyzed Cross-coupling Reactions

IASOC, Ischia September 16-22, 2006

Transition Metal-catalyzed Cross-coupling reactions

Pd, Ni, Cu

➢ **For Industrial Applications :**

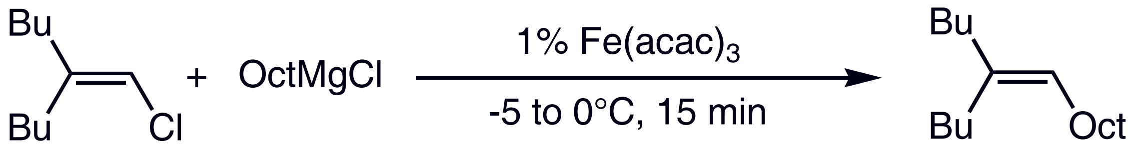
- Toxicity
- Treatment of effluents
- Cost (metal and ligand)

➢ **Is it reasonable to use only two or three metals to perform all coupling reactions ?**

- Is it possible to avoid the use of sophisticated ligand by changing the metal

⇒ **Search for alternative procedures (Fe, Mn and Co-catalyzed reactions)**

Iron-catalyzed Alkenylation of Grignard Reagents

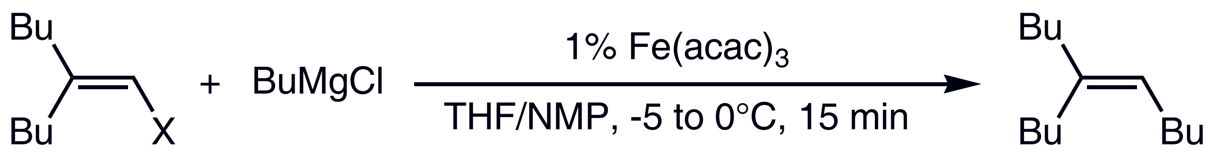


Solvent	**Yield (%)**
THF	< 5
THF/NMP*	85

* 9 equiv. based on OctMgCl.

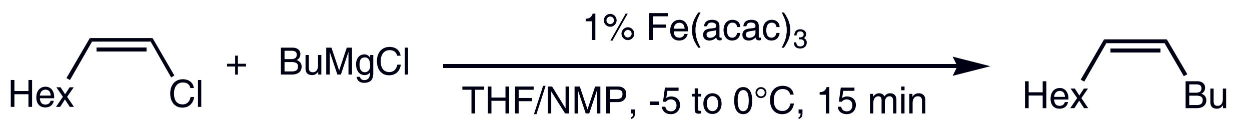
G. Cahiez, G.; Avedissian, H. *Synthesis*, **1998**, 1199.

Nature of the Leaving Group

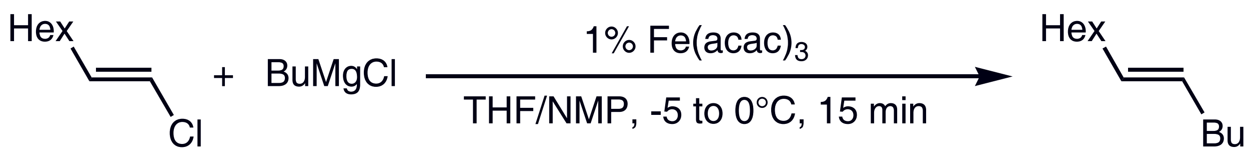


X	Yield(%)
I	82
Br	83
Cl	85

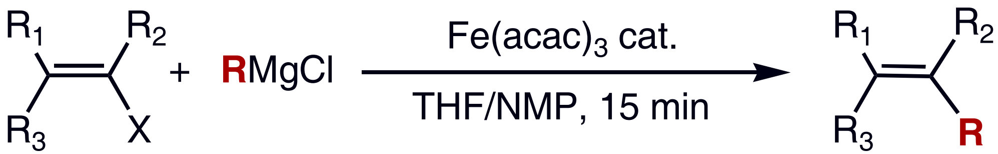
Stereoselectivity

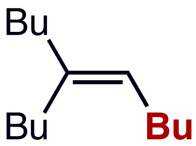


80%, *Z* ≥ 99.5%

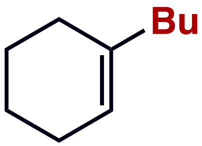


75%, *E* ≥ 99.5%

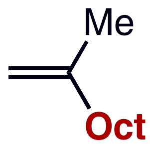




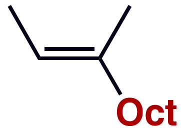
X= Cl ; **82%**



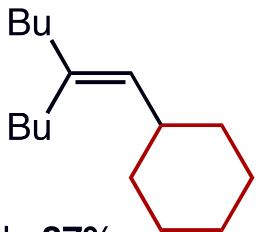
X= Cl ; **75%**



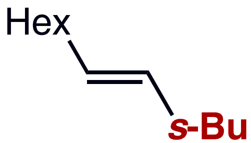
X= Br ; **86%**



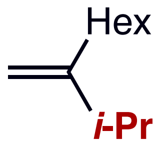
X= Br ; **84%**



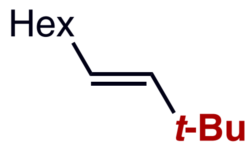
X= Cl ; **87%**



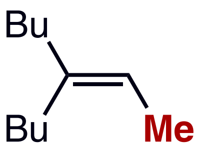
X= I ; **80%**



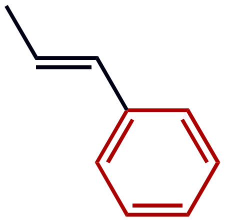
X= Br ; **72%**



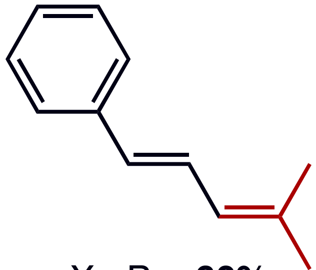
X= Br ; **64%****



X= I ; **75%**



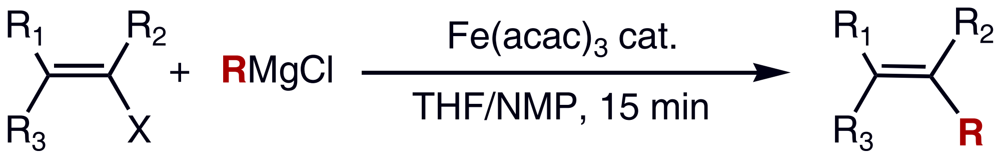
X= Br ; **82%***

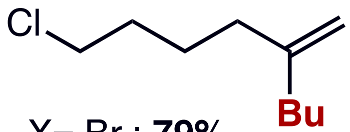


X= Br ; **60%**

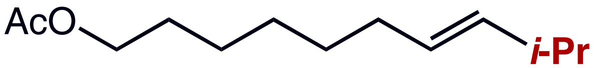
* Sulfolane. ** Fe(dpm)$_3$

Chemoselectivity

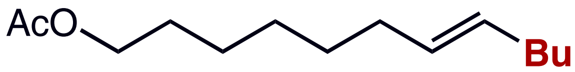




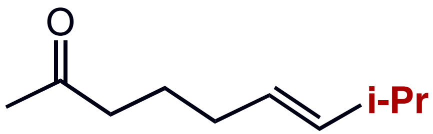
X= Br ; **79%**



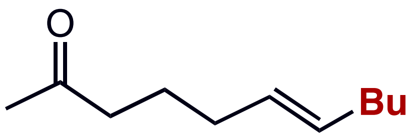
X= Cl ; **72%**



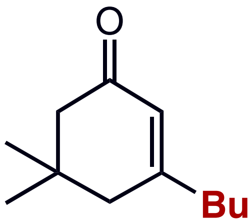
X= Cl ; **80%**



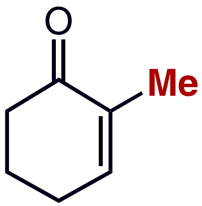
X= Cl ; **80%**



X= Cl ; **72%**

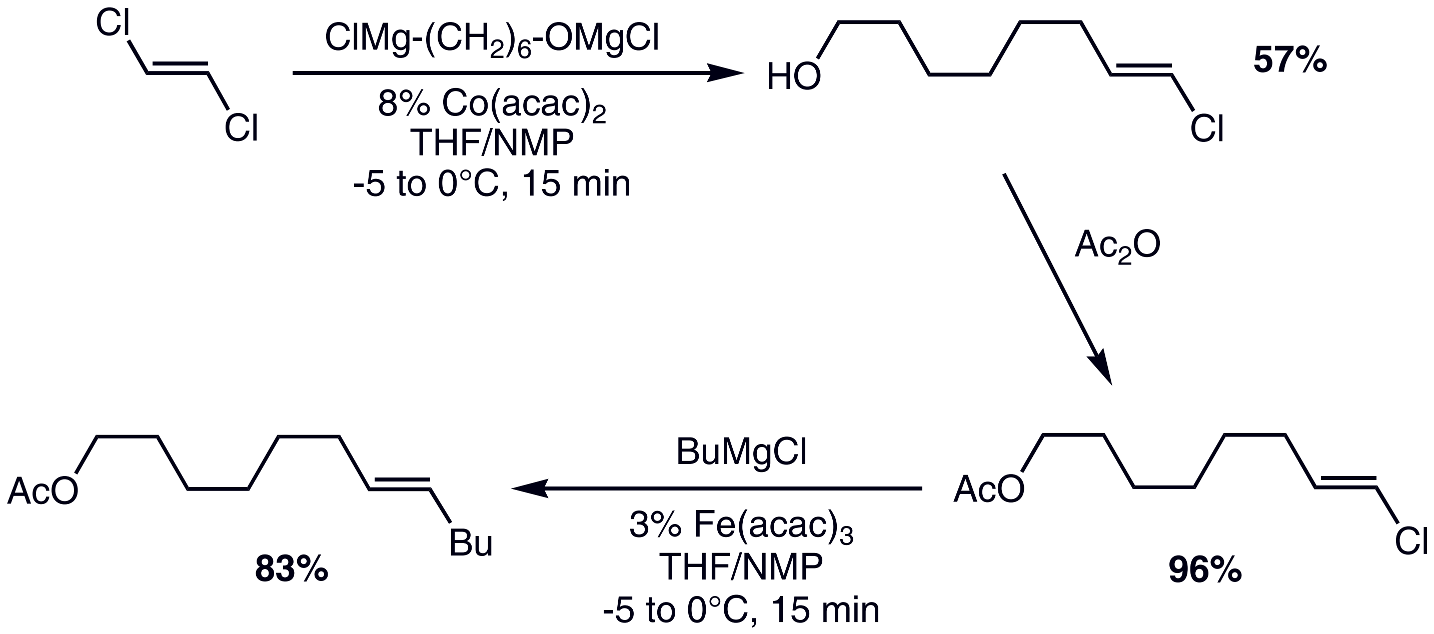


X= Cl ; **79%**

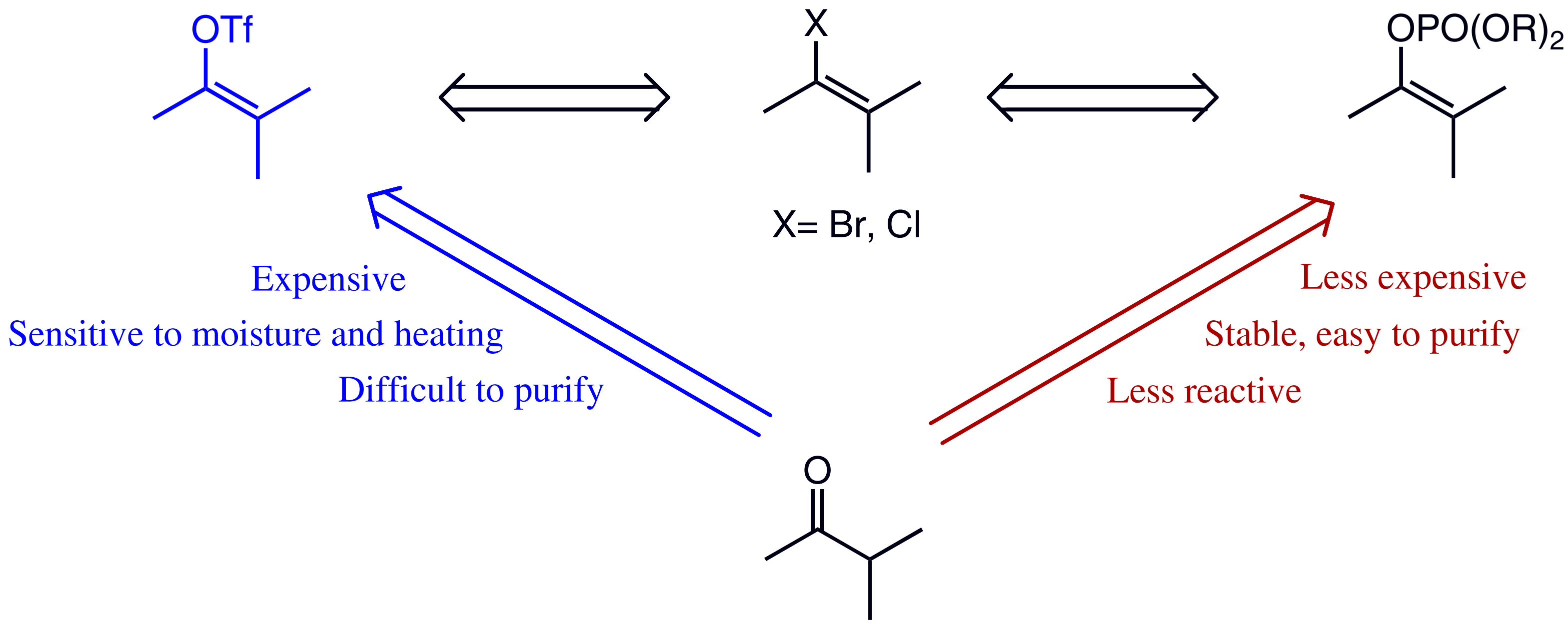


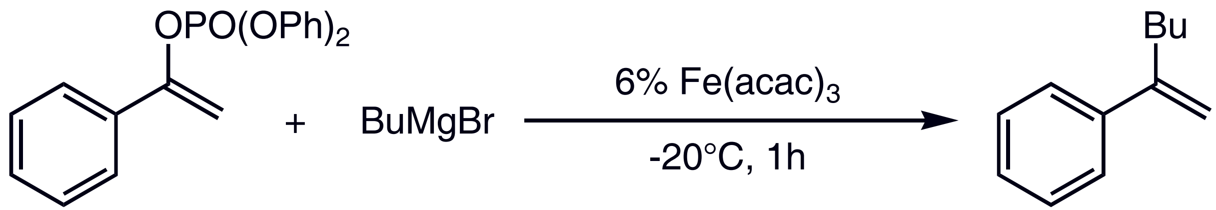
X= I ; **68%**

Synthesis of the Pheromone of Argyroplace (chryptophlebia) Leucotetra



Looking for an Alternative to Alkenyl Halides

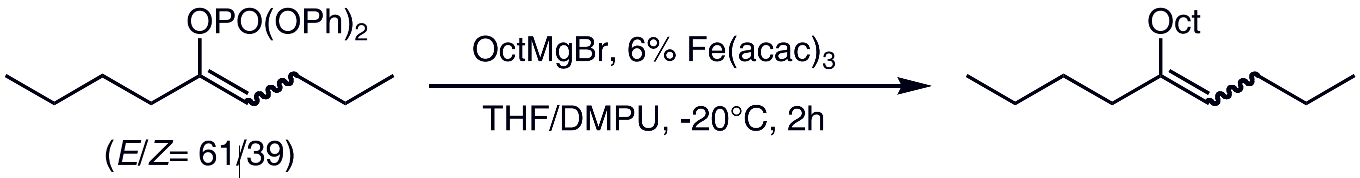


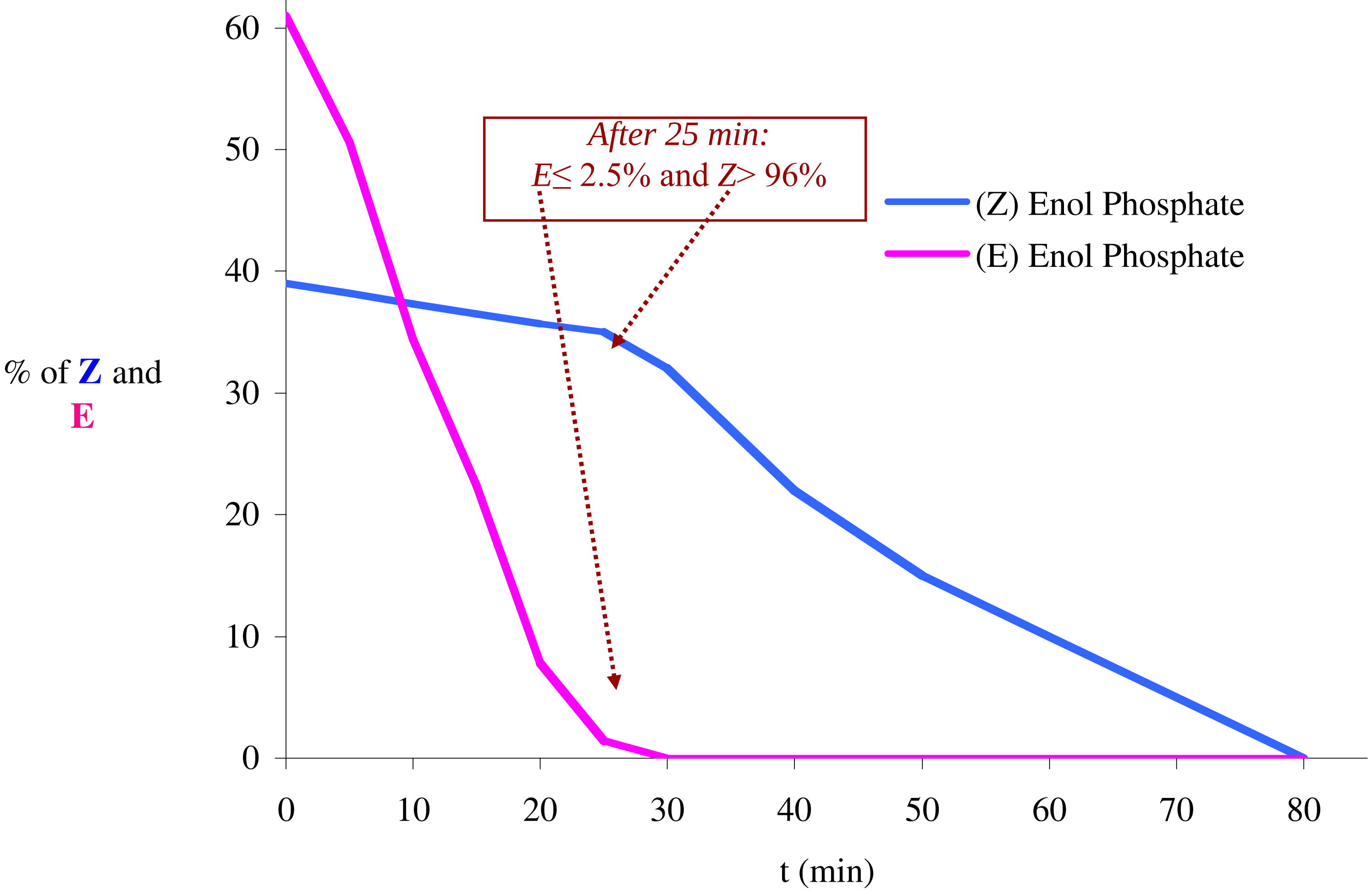


THF: 90%

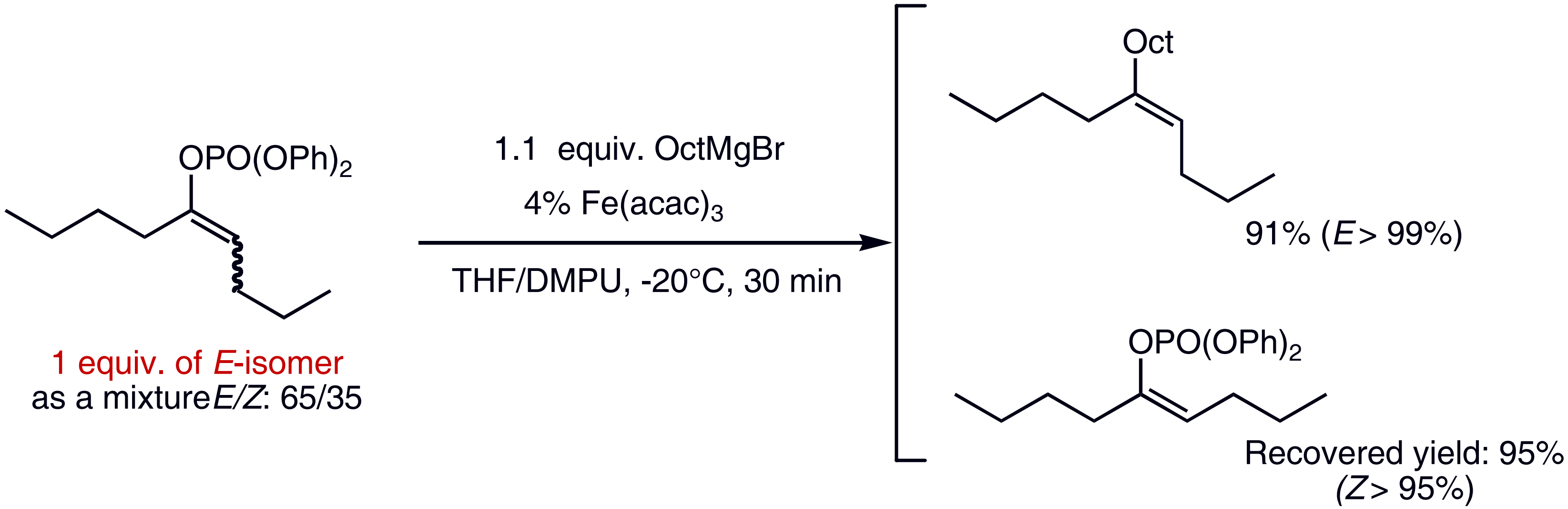
THF/NMP: 91%

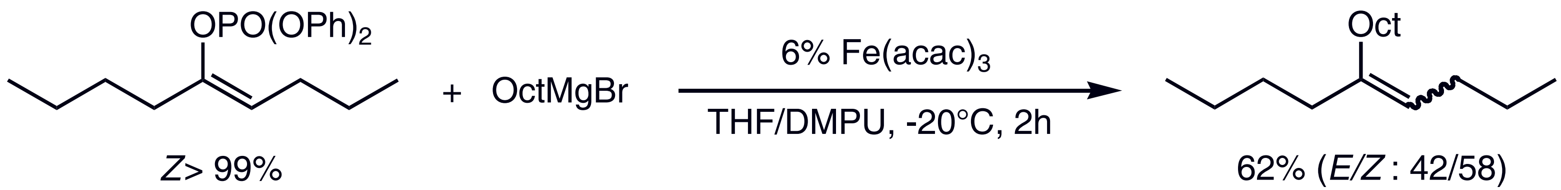
Reactivity of (E)- and (Z)-Enol Phosphates



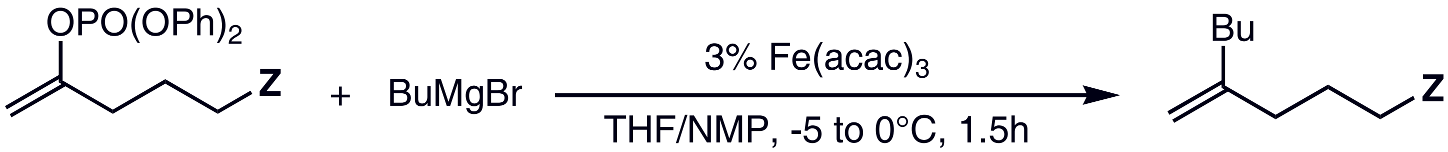


Stereoselectivity of the Reaction

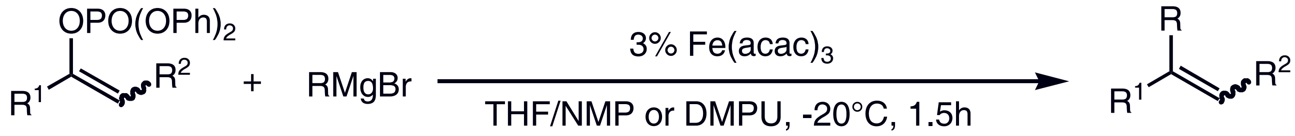


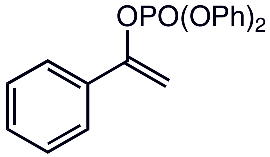
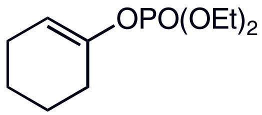
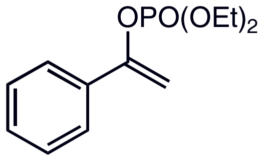
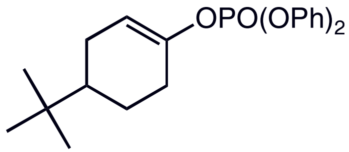
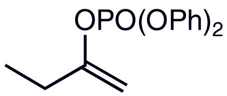
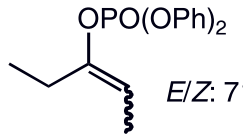
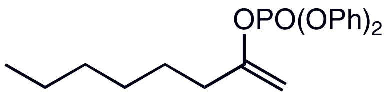
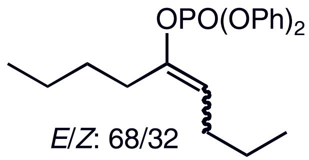
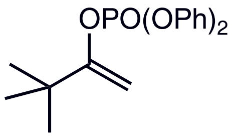
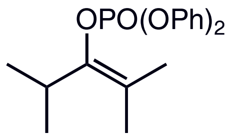


Chemoselectivity

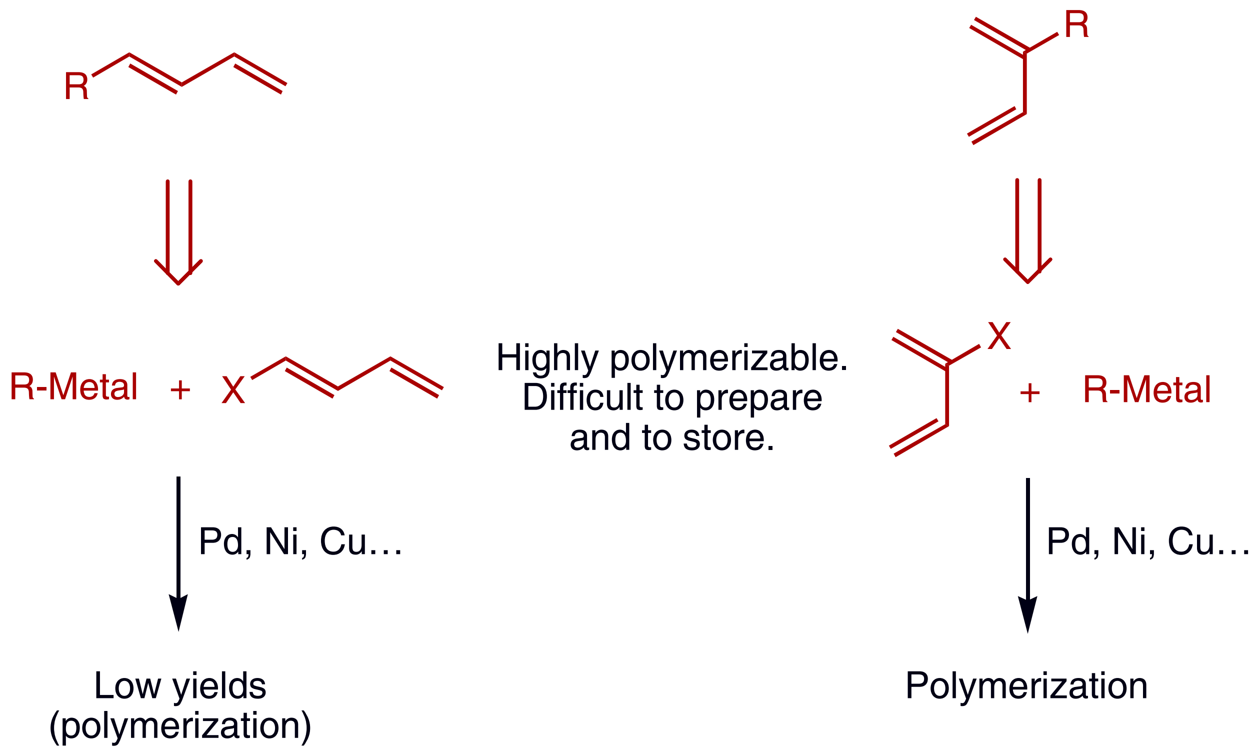


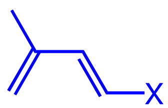
Z	Yield (%)
Cl	85
Br	0
CN	96
COOMe	84

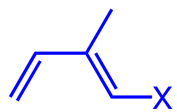


Enol Phosphate	RMgX	Cosolvent	Yield (%)	Enol Phosphate	RMgX	Cosolvent	Yield (%)
	BuMgCl	None	90		OctMgCl	"	90
	BuMgCl	NMP	91		OctMgCl	"	93
	OctMgCl *c*-HexMgCl	"	82 20	 *E*/*Z*: 71/29	OctMgCl PhMgCl	DMPU	81 (*E*>99%) 73 (*E*□ 95%)
	BuMgBr	"	75		PhMgCl *t*-BuMgCl	"	70 (*E*> 95%) 0
	OctMgCl	"	73		BuMgCl	"	10

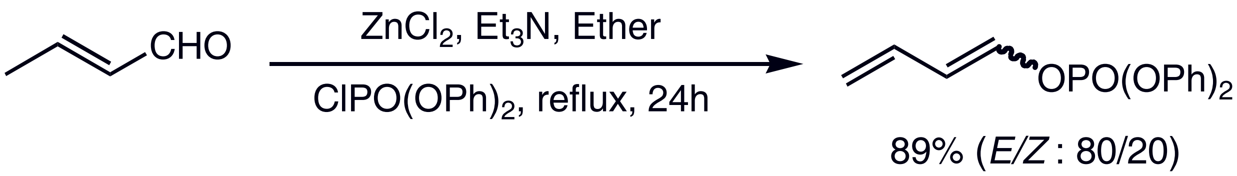
Preparation of Terminal Dienes



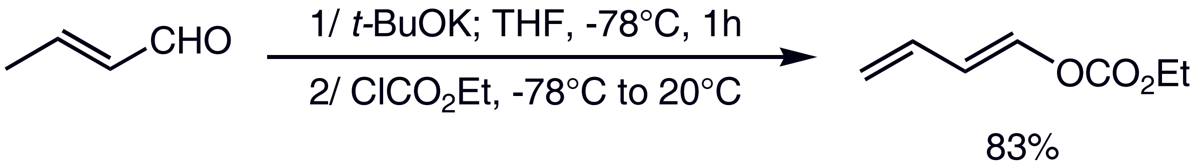
- **Similar results with** 

and 

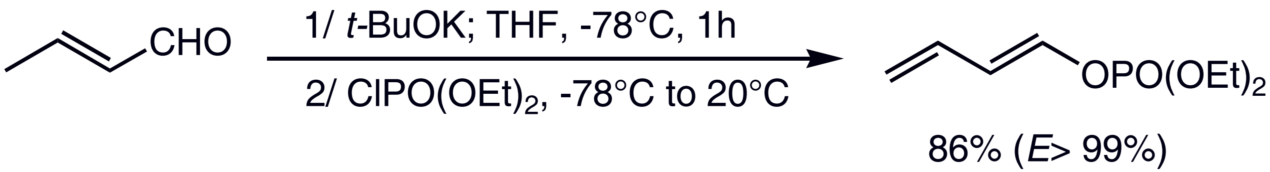
Preparation of Dienol Phosphates from α,β-Ethylenic Aldehydes



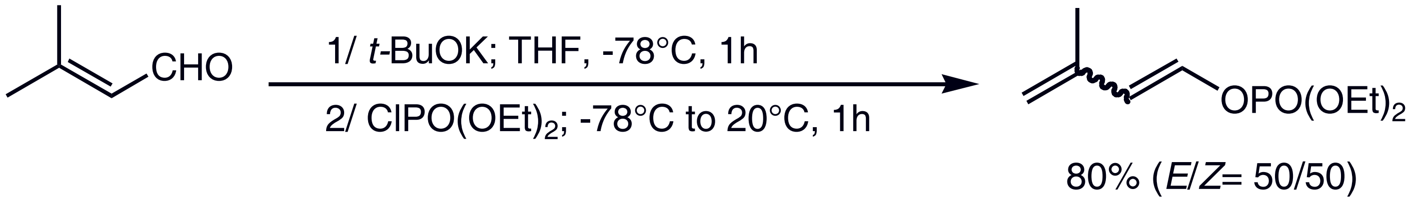
Gaonac'h, O.; Maddaluno, J.; Chauvin, J.; Duhamel, L. *J. Org. Chem.* **1991**, 56, 4045-4048

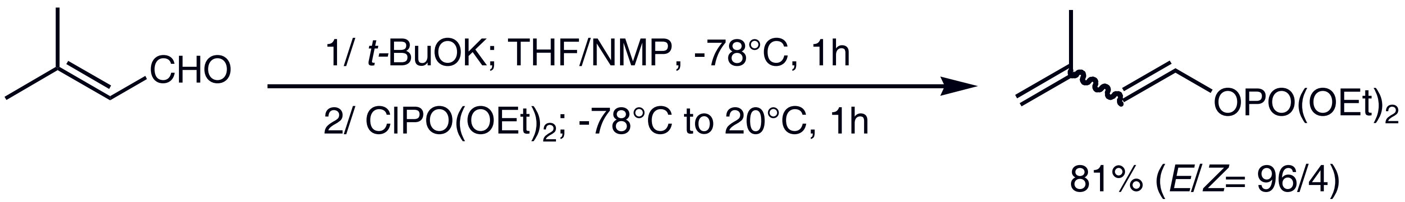


De Cusati, P. F.; Olofson, R. A. *Tetrahedron Lett.* **1990**, 31, 1405-1408

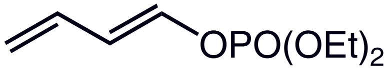
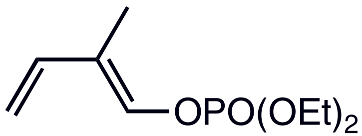
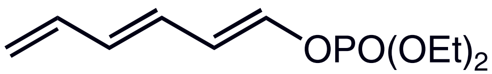
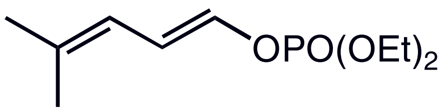


Preparation of Dienol phosphates from α,β-Ethylenic Aldehydes

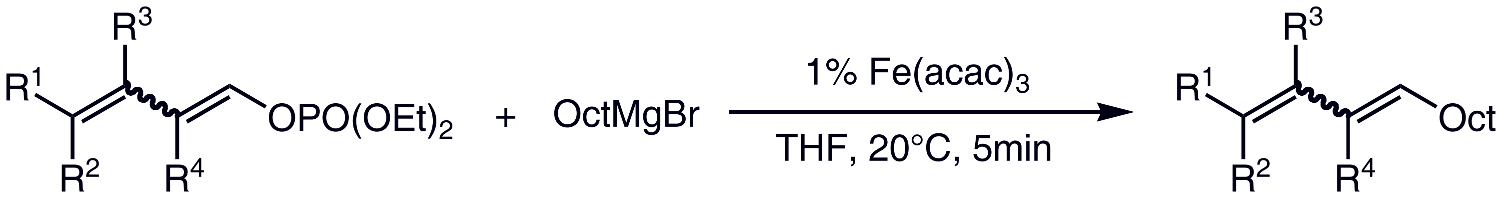


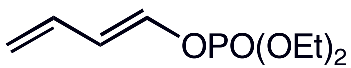
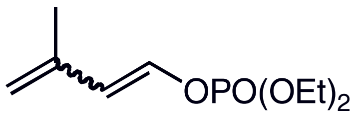
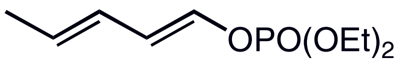
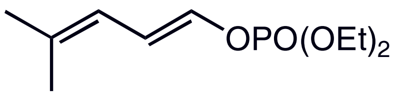


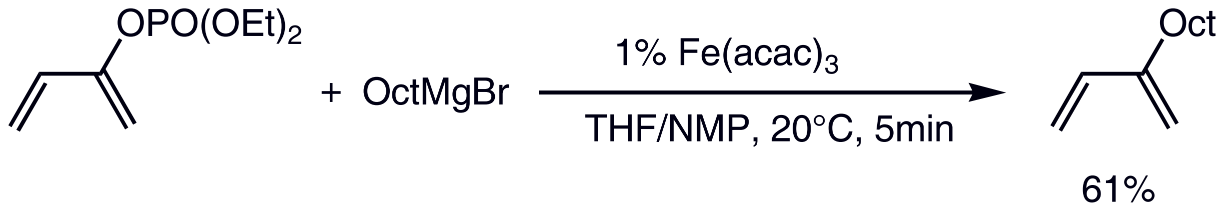
Stereoselective Preparation of Dienol Phosphates from α,β-Ethylenic Aldehydes

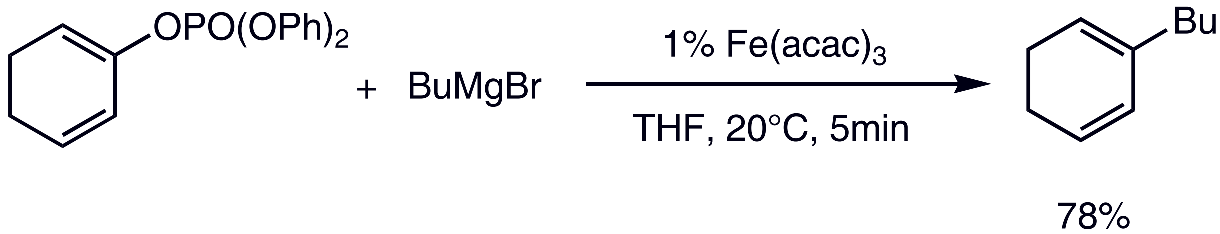
Dienol Phosphate	**Yield (%)**	**Stereoselectivity**
	86	*E*> 99%
	81	*E*≥ 96%
	84	*E*> 99%
	58	*E,E*> 99%
	78	*E*> 99%

Use of Dienol Phosphates to Prepare Terminal Dienes

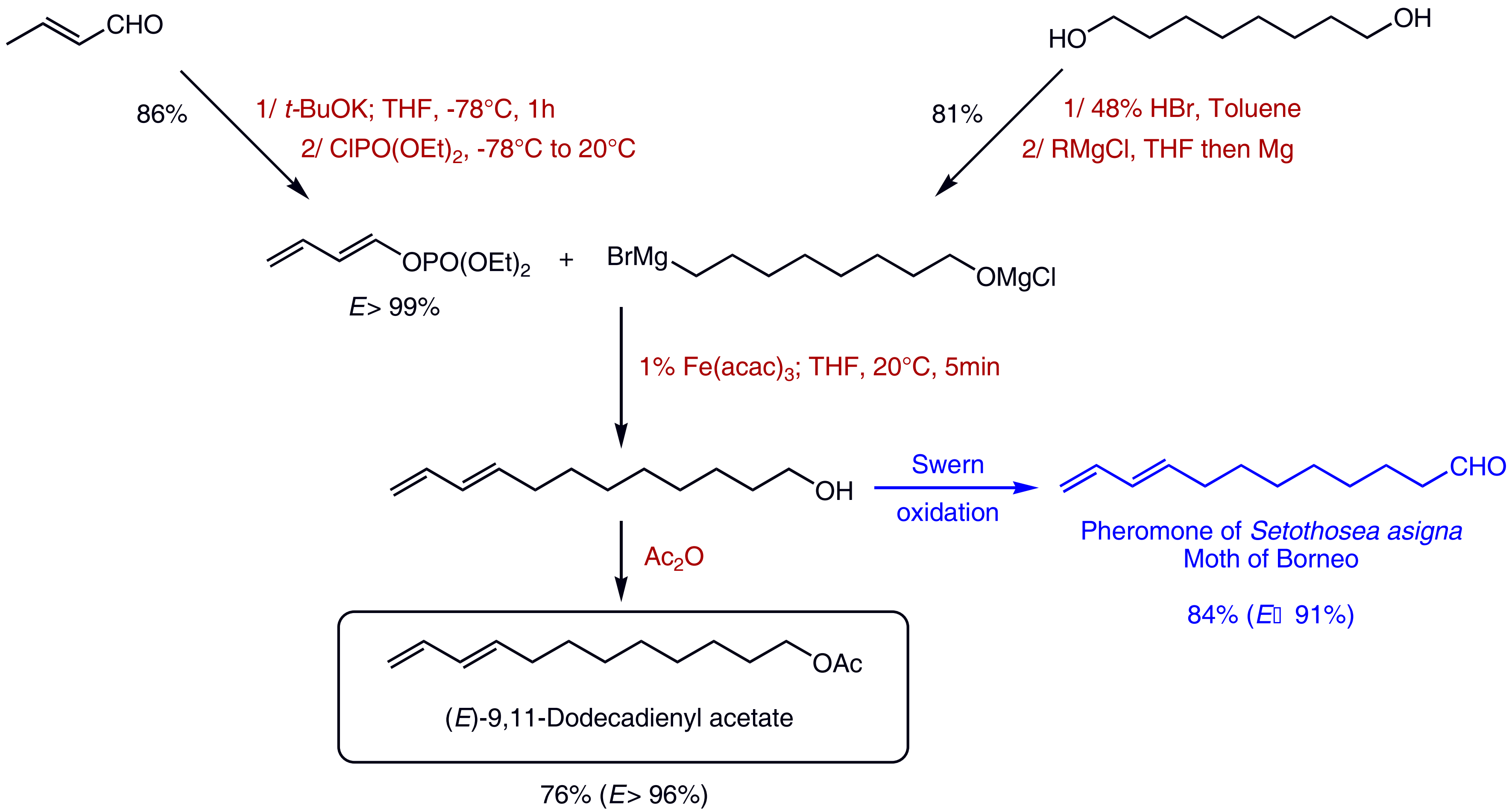


Starting Dienol Phosphate	**Yield (%)**	**Stereoselectivity**
	92	*E* ≥ 98%
 *Z* ≥ 96%	85	*E* > 90%
	88	*E,E* > 99%
 *E,E* = 91%	90	*E,E* ≥ 93%
	93	*E* ≥ 99%

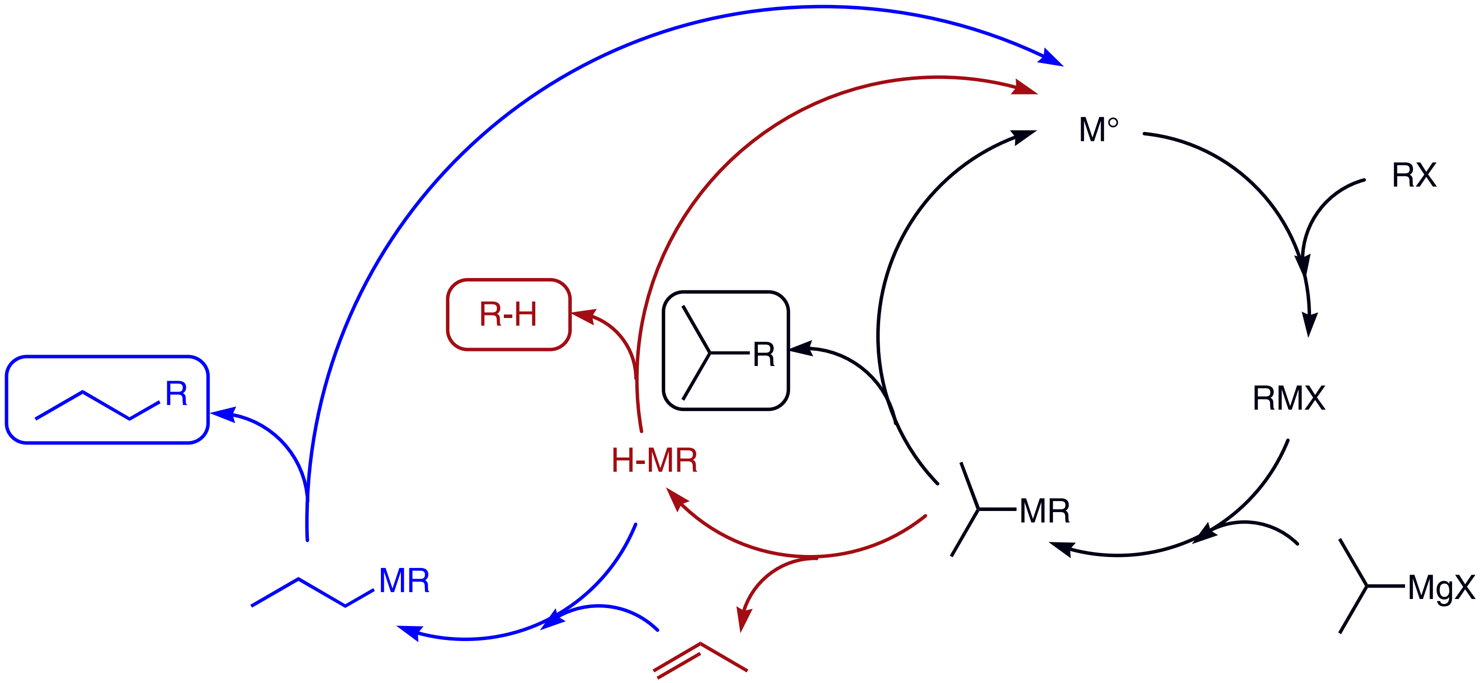

OPO(OEt)2
+ OctMgBr
1% Fe(acac)3
THF/NMP, 20°C, 5min
Oct
61%


OPO(OPh)2
+ BuMgBr
1% Fe(acac)3
THF, 20°C, 5min
Bu
78%

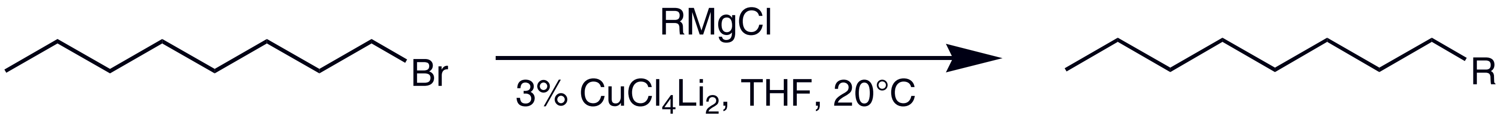
Synthesis of the Pheromone of Diparopsis Castanea Red-Bollworm Moth



Transition Metal-catalyzed Cross-coupling Reactions Using Secondary Aliphatic Grignard Reagents



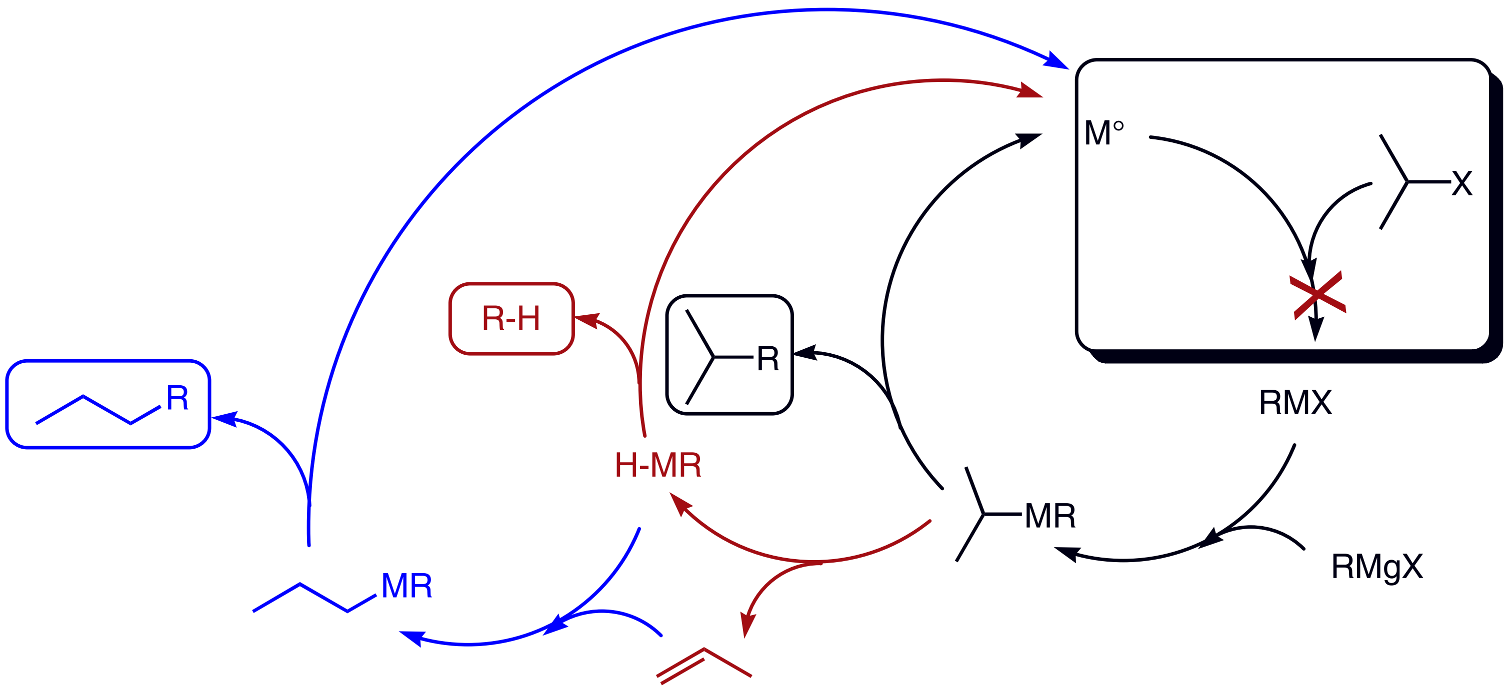
Alkyl-Alkyl Coupling from Secondary Aliphatic Grignard Reagents



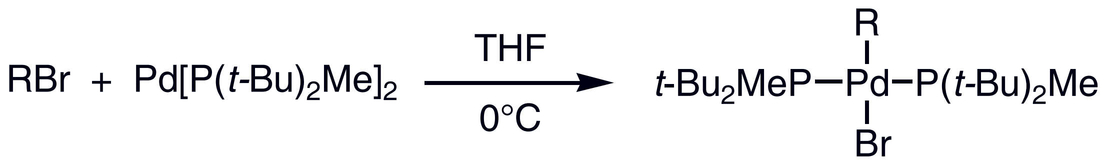
R = *t*-Bu	THF :	8%
	THF, 4 equiv. NMP :	85%
R = *i*-Pr	THF :	5%
	THF, 4 equiv. NMP :	76%

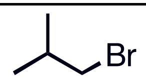
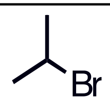
Cahiez, G.; Chaboche, C.; Jézéquel, M. *Tetrahedron* **2000**, *56*, 2733.

Transition Metal-catalyzed Cross-coupling Reactions from Secondary or Tertiary Alkyl Halides



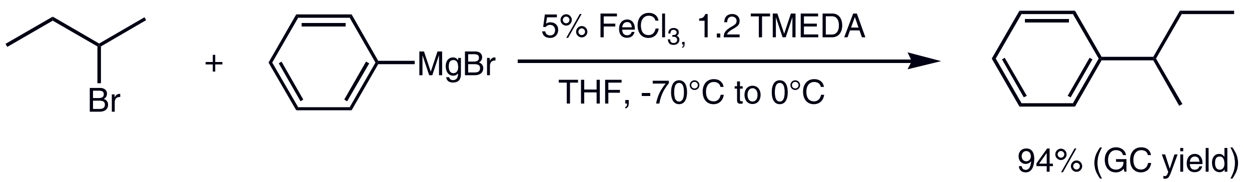
Oxydative Addition of n- and s-Alkyl Halides



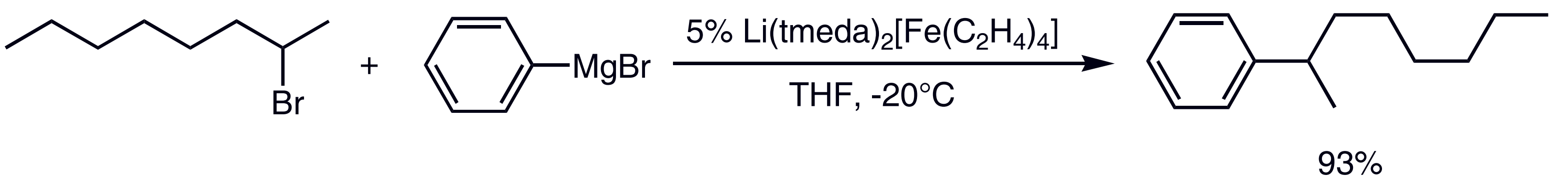
RBr	k_{rel}	ΔG^{-} (kcal mol^{-1})
	1	19.5
	0.054	21
	< 0.0001	> 24

Hills, I. D.; Netherton, M. R.; Fu, G. C. *Angew. Chem. Int. Ed.* **2003**, *42*, 5749.

Iron-catalyzed Arylation of n- or s-Alkyl Halides

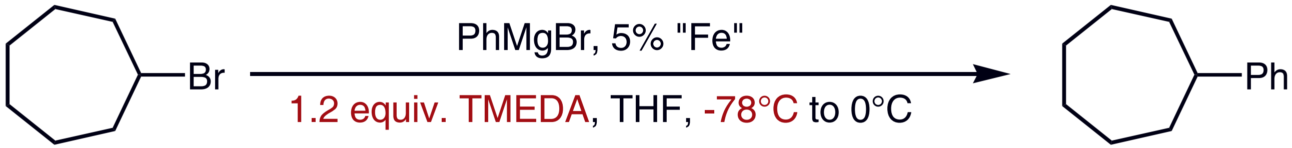


Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, 126, 3686.



Martin, R.; Fürstner, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 3955.

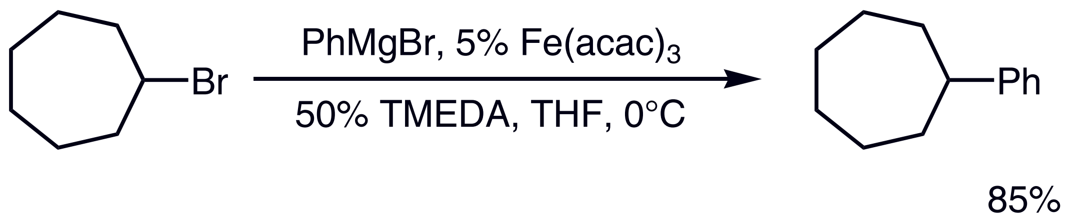
Iron-catalyzed Arylation of n- or s-Alkyl Halides



$FeCl_3$: 71%
$Fe(acac)_3$: 14%

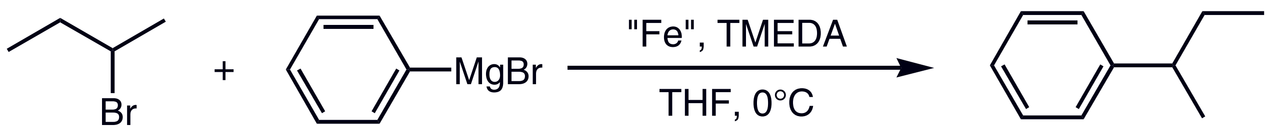
Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, 126, 3686.

Iron-catalyzed Arylation of n- or s-Alkyl Halides



Nakamura conditions: 5% Fe(acac)$_3$, 120% TMEDA, -78°C to 0°C : 14% (GC yield)

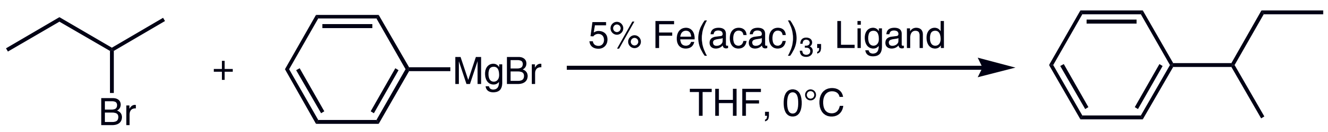
Nature of the catalyst



% "Fe"	% TMEDA	Yield (%)
5% $FeCl_3$ (98%, Across Chemical)	120	85
5% $FeCl_3$ (97%, Aldrich Chemical)	"	76
5% $FeCl_3$ (99.9%, Aldrich Chemical)	"	77
5% $Fe(acac)_3$ (99%, Across Chemical)	120	90
	50	90

Nakamura:
94% (GC)

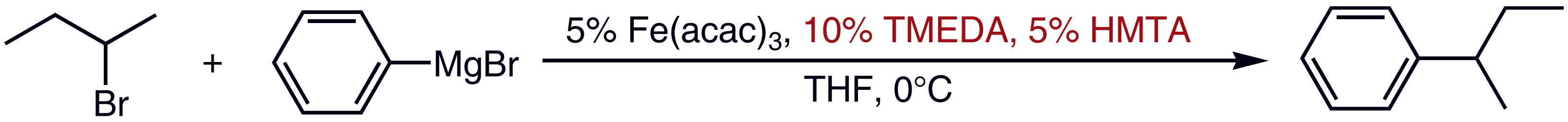
Nature of the Ligand



Ligand	% of ligand	Yield (%)
TMEDA	50	90
	10	60
HMTA	50	75
	5	80
	2.5	55

HMTA= Hexamethylenetetramine: $(CH_2)_6N_4$

A New Catalytic System

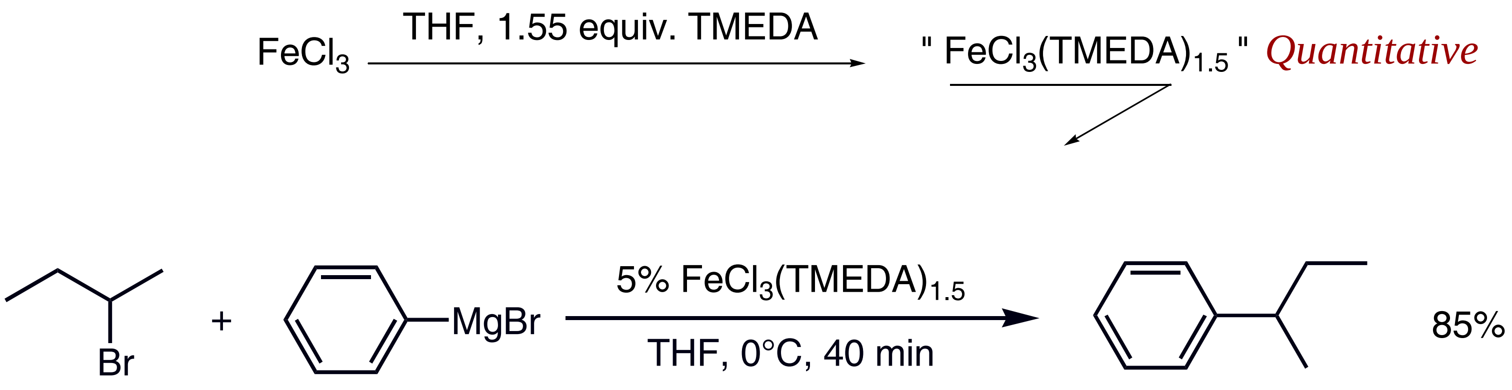


93%

On a 0.25 mole scale: 88%

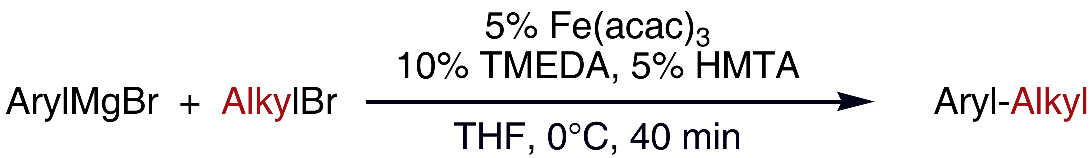
50% TMEDA: 90%
5% HMTA: 80%

Is It Possible to Use $FeCl_3$?

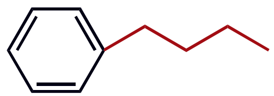


- **7.5% TMEDA instead of 120% !**
- **$FeCl_3(TMEDA)_{1.5}$ is a non hygroscopic material contrary to $FeCl_3$!**

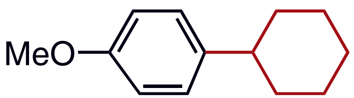
Iron-catalyzed Arylation of Alkyl Halides



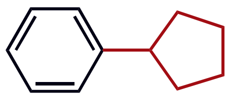
76%



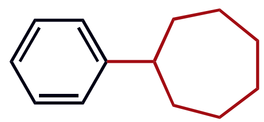
92%



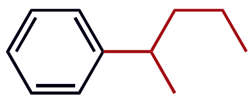
89%



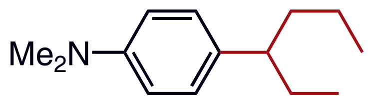
91%



85%

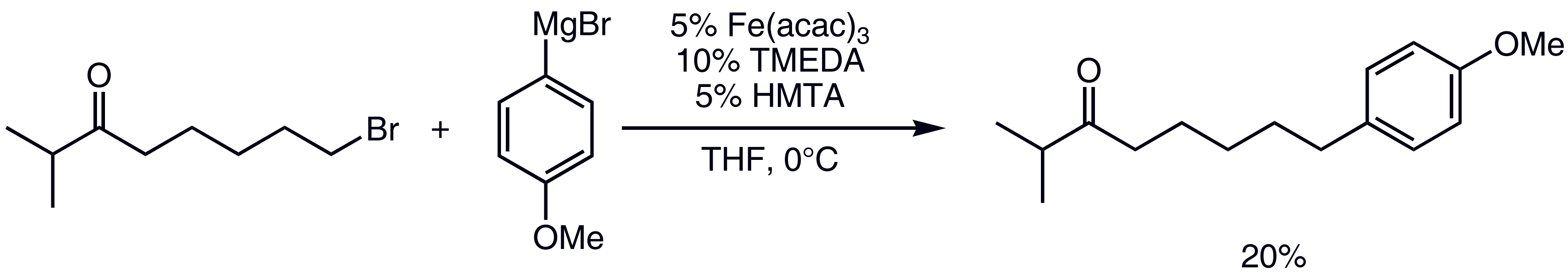


93%

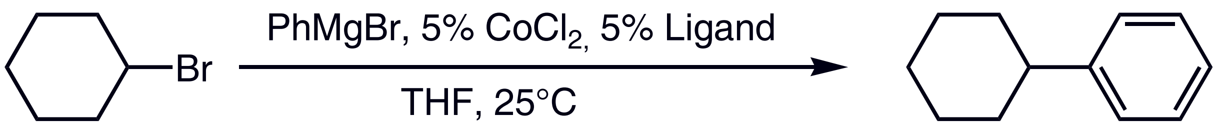


71%

Iron-catalyzed Arylation of Alkyl Halides: Chemoselectivity



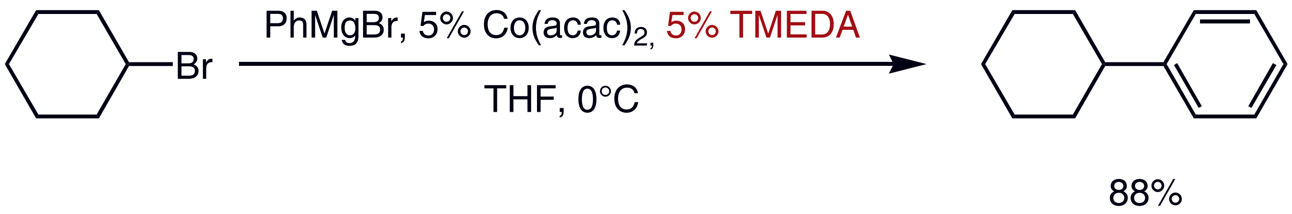
Cobalt-catalyzed Arylation of s-Alkyl Halides



Ligand	**Yield (%)**
	95
TMEDA	43

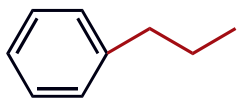
Ohmiya, H.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2006**, *128*, 1886.

Cobalt-catalyzed Arylation of s-Alkyl Halides

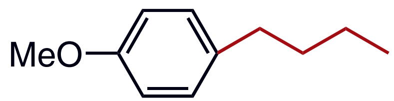


Cobalt-catalyzed Arylation of Alkyl Halides

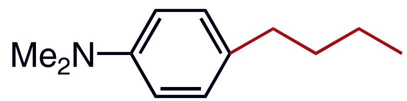
ArylMgX + AlkylBr $\xrightarrow[\text{THF, 0°C, 40 min}]{\text{5\% Co(acac)}_3\text{, 5\% TMEDA}}$ Aryl-Alkyl



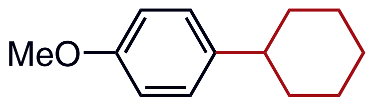
86%



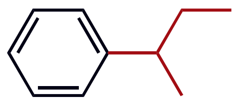
91%



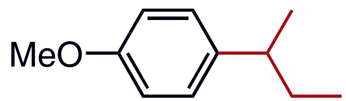
96%



95%

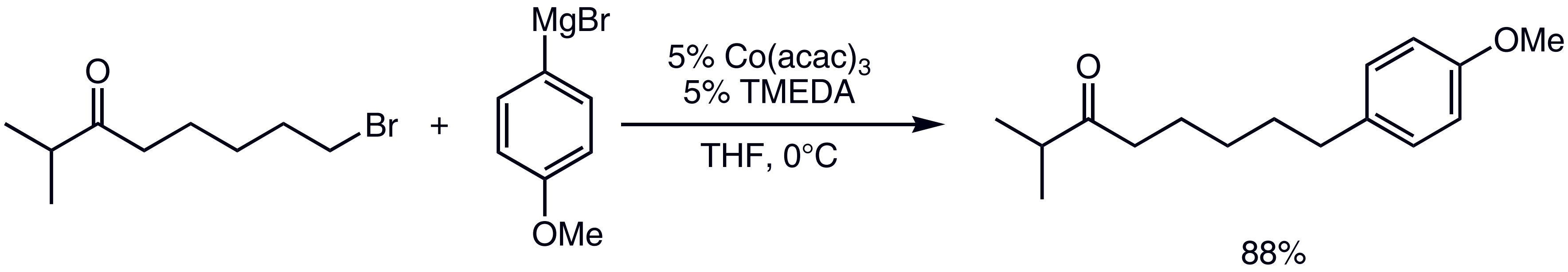


93%

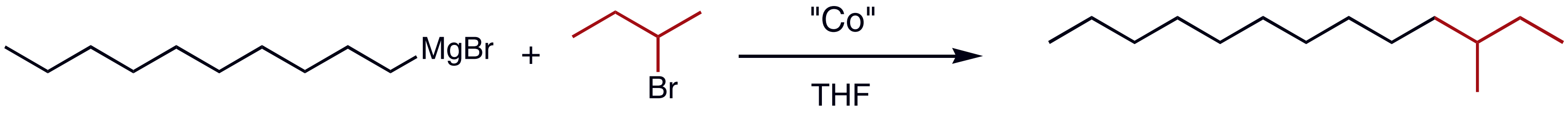


92%

Cobalt-catalyzed Arylation of Alkyl Halides: Chemoselectivity



Cobalt-catalyzed Alkyl-Alkyl Cross-coupling Reaction from Secondary Alkyl Halides



Catalyst	Ligand	Temperature	Yield
$CoCl_2$	4 TMEDA	10	35
CoI_2	"	"	50
$CoCl_2$ 2LiI	**"**	**"**	**79**
$CoI_2 \cdot 2LiCl$	"	"	54
$CoCl_2 \cdot 2LiI$	"	-20	< 5
"	"	25	45
"	2 TMEDA	10	60
"	10 TMEDA	"	79

Cobalt-catalyzed Alkyl-Alkyl Cross-coupling Reaction from Secondary Alkyl Halides