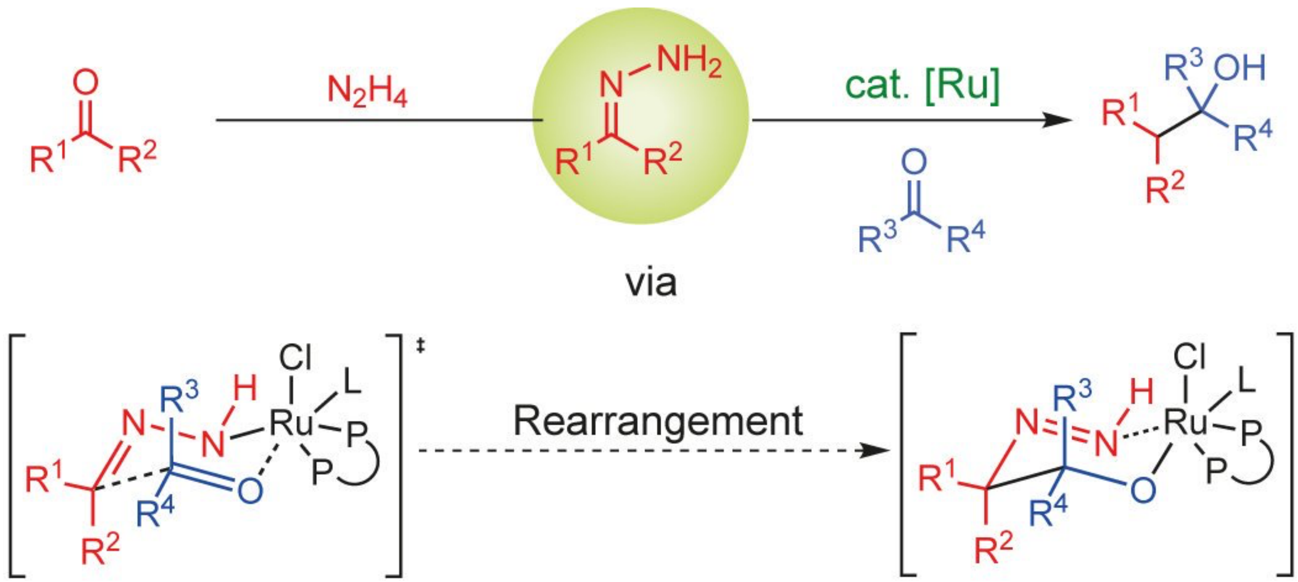
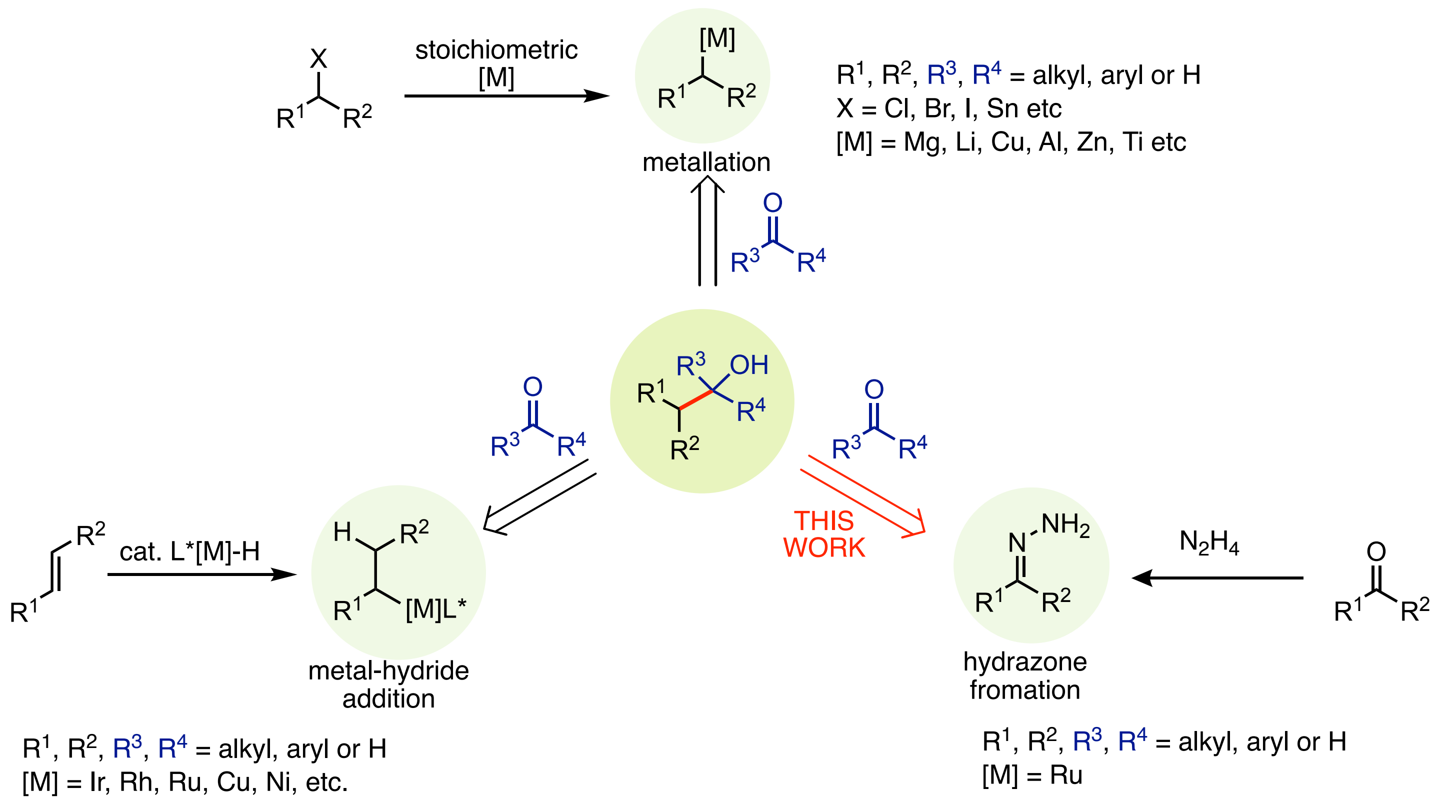
Aldehydes as alkyl carbanion equivalents for additions to carbonyl compounds.



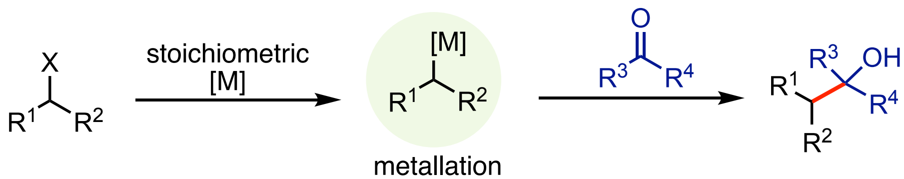
Haining Wang, Xi-Jie Dai and Chao-Jun Li, *Nat Chem.* DOI:10.1038/nchem.2677

Steph McCabe
Wipf Group Current Literature 03/04/2017

Strategies to Access 2° and 3° Alcohols by Carbonyl Addition



Strategies to Access 2° and 3° Alcohols by Carbonyl Addition

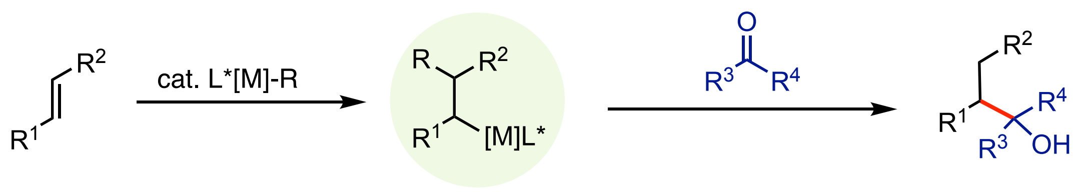


R^1, R^2, R^3, R^4 = alkyl, aryl or H
X = Cl, Br, I, Sn etc
[M] = Mg, Li, Cu, Al, Zn, Ti etc

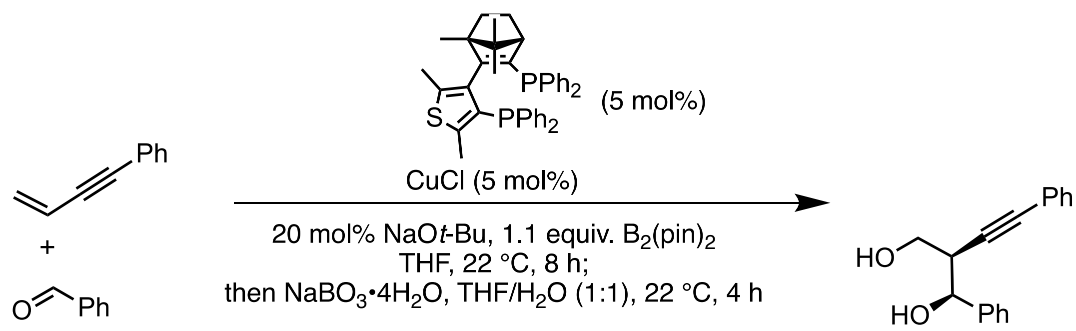
Limitations:

- Stoichiometric, pre-formed organometallic reagents
- Air & moisture sensitive
- Copious metal waste
- Pre-synthesis of organohalide substrates
- high nucleophilicity and basicity (= poor selectivity)

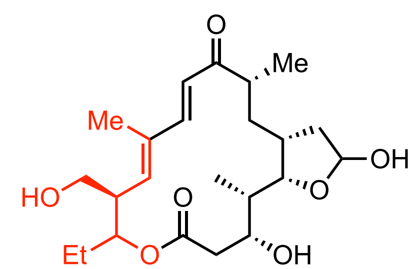
Strategies to Access 2° and 3° Alcohols by Carbonyl Addition



copper-catalysed borylative enantioselective additions



76%, 98:2 *dr*
95:5 *er*

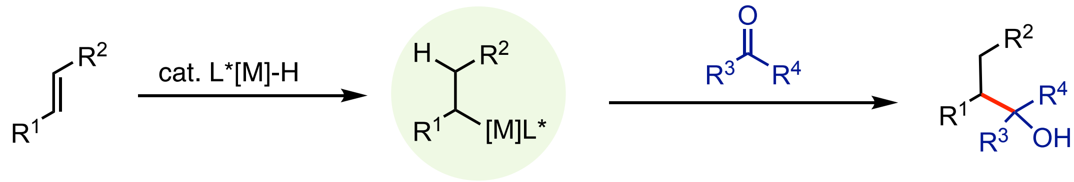


tylonolide

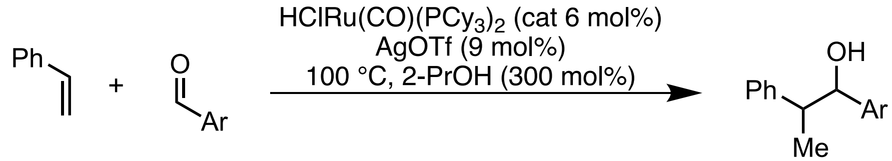
JACS, **2014**, *136*, 11304 (Hoyveda)

Strategies to Access 2° and 3° Alcohols by Carbonyl Addition

metal-hydride addition

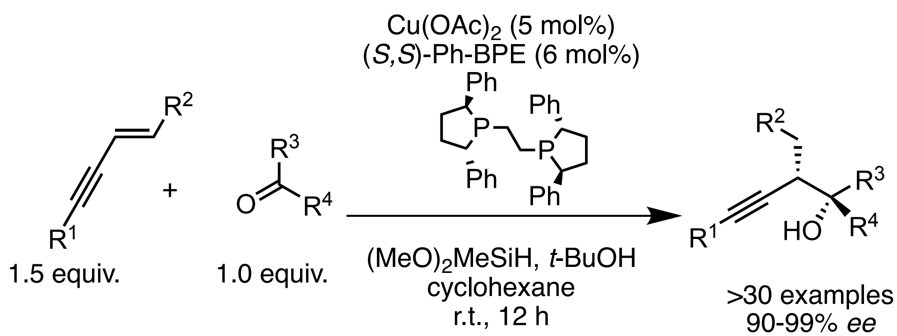


Ru-catalyzed reductive coupling

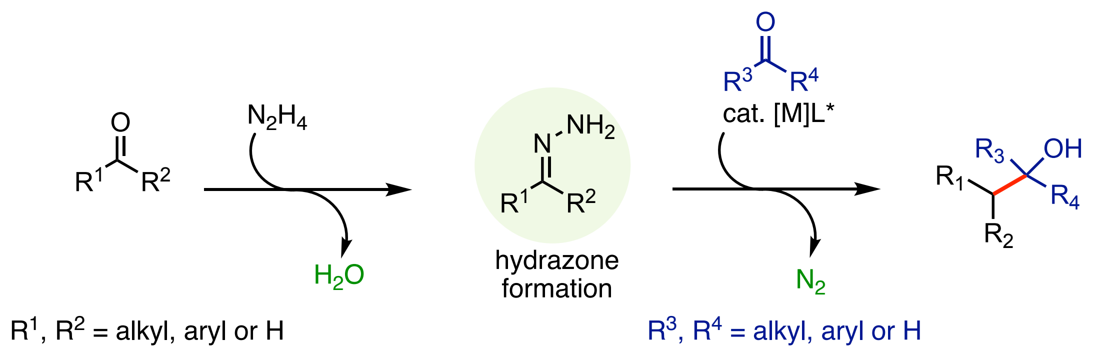


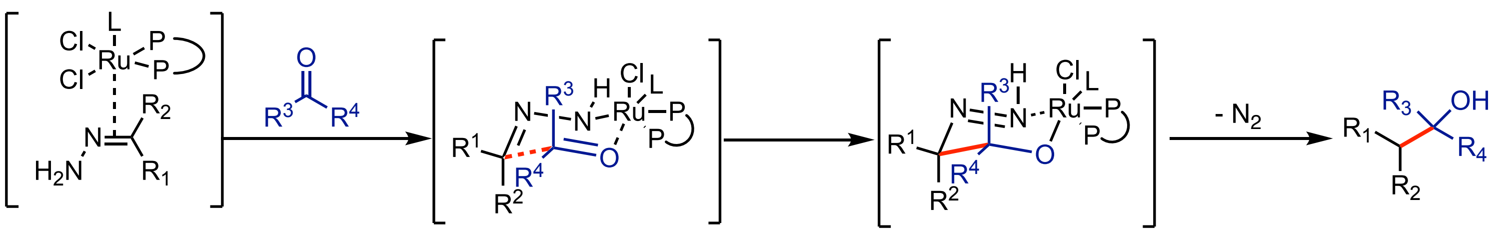
ACIE, **2016**, *55*, 16119 (Krische)

diastereoselective ketone 1,2-addition addition of enantioenriched cuprates

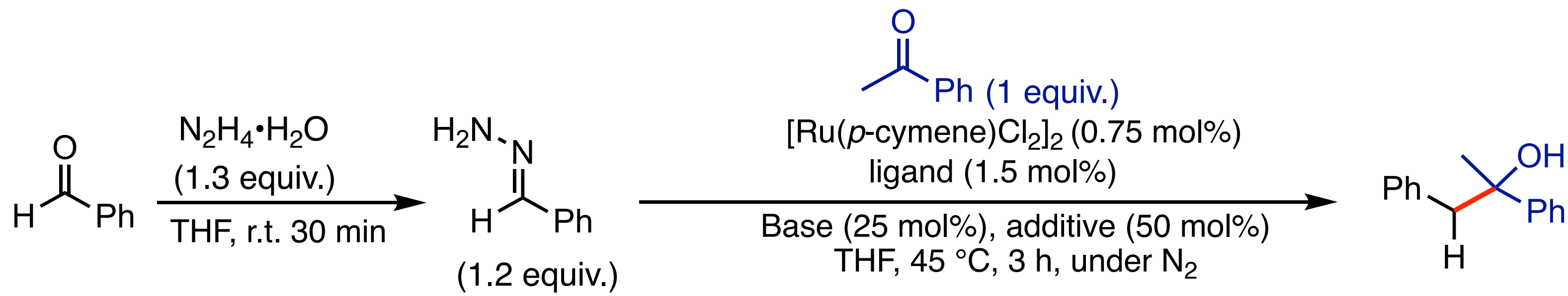


Science, **2016**, *353*, 144 (Buchwald)

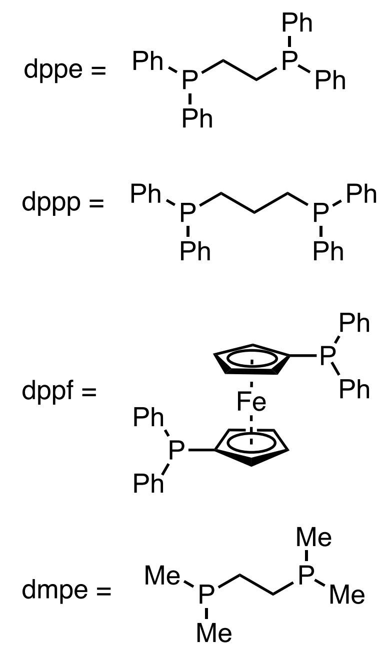

O
R1 R2
N2H4
H2O
N NH2
R1 R2
hydrazone
formation
O
R3 R4
cat. [M]L*
N2
R3 OH
R1 R4
R2
R1, R2 = alkyl, aryl or H
R3, R4 = alkyl, aryl or H


Cl L P
Ru
Cl P
R2
N
H2N R1
O
R3 R4
R3 H Cl L
N N Ru P
R1 O P
R4
R2
Zimmerman-Traxler TS
R3 H Cl L
N N Ru P
R1 O P
R4
R2
- N2
R3 OH
R1 R4
R2

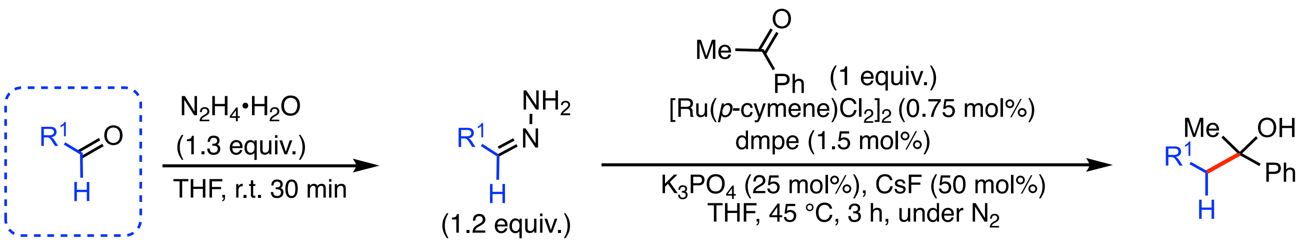
Optimization



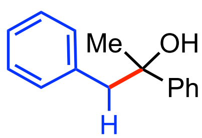
Entry	Ligand	Base	Additive	Yield (%)
1	-	K_3PO_4	CsF	13
2	dppe	K_3PO_4	CsF	78
3	dppp	K_3PO_4	CsF	92
4	dppf	K_3PO_4	CsF	58
5	dmpe	-	CsF	3
6	dmpe	K_2CO_3	CsF	57
7	dmpe	Cs_2CO_3	CsF	51
8	dmpe	KO^tBu	CsF	82
9	dmpe	K_3PO_4	CsF	95
10	dmpe	K_3PO_4	-	85



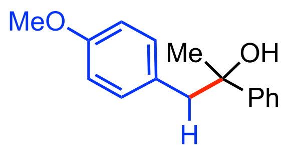
Substrate Scope: Hydrazone Precursor Carbonyl



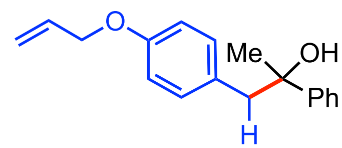
Aromatic aldehydes



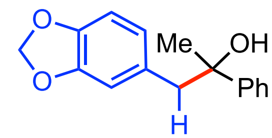
94%



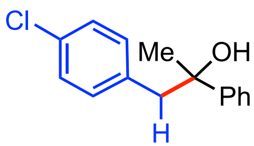
58%



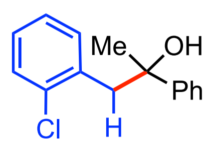
98%



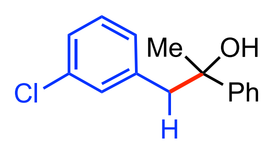
86%



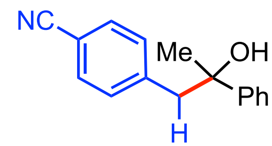
85%



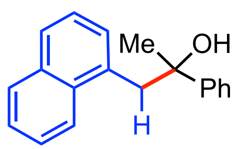
65%



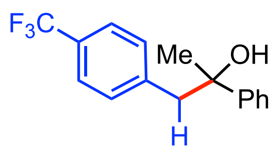
94%



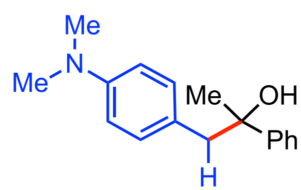
43%



97%

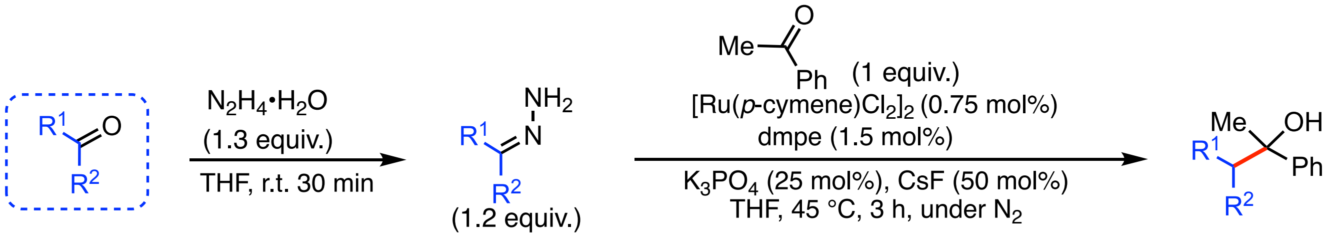


95%

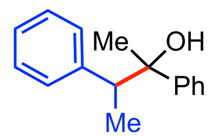


67%

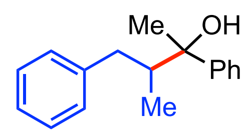
Substrate Scope: Hydrazone Precursor Carbonyl



ketones

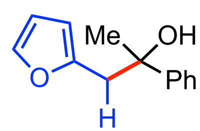


30% (*80 °C, 20 h, K-O*t*Bu)

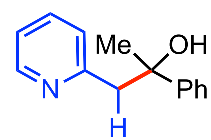


23% (*80 °C, 20 h, , K-O*t*Bu)

heterocyclic aldehydes

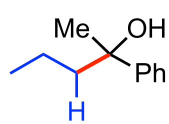


75%



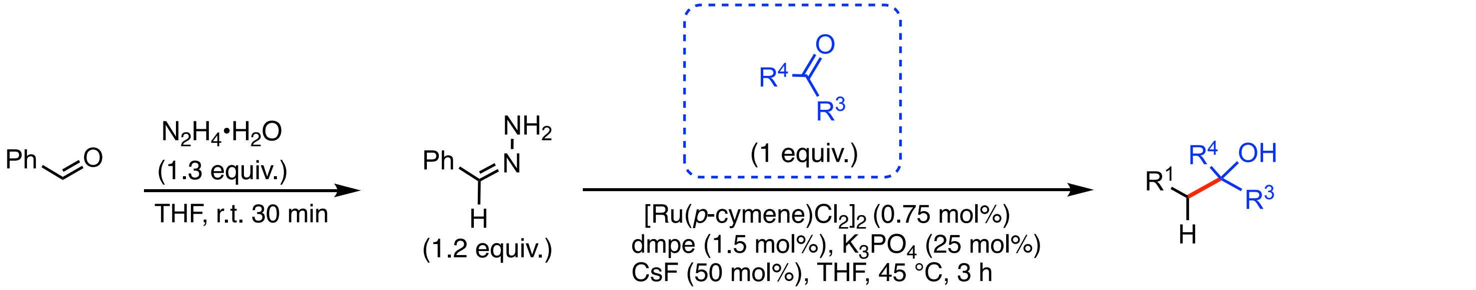
53%

aliphatic aldehyde

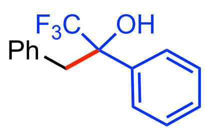


20%

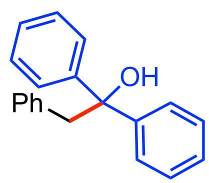
Substrate Scope: Electrophilic Carbonyl



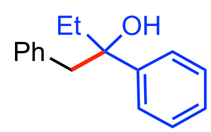
aromatic ketones



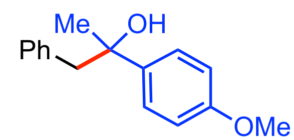
89%



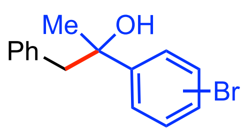
65%



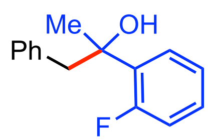
93%



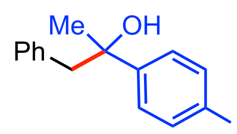
93%



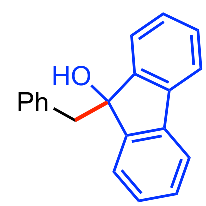
p-Br, 86%
o-Br 71%



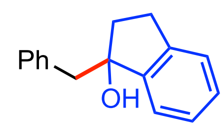
84%



79%

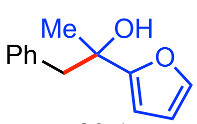


76%



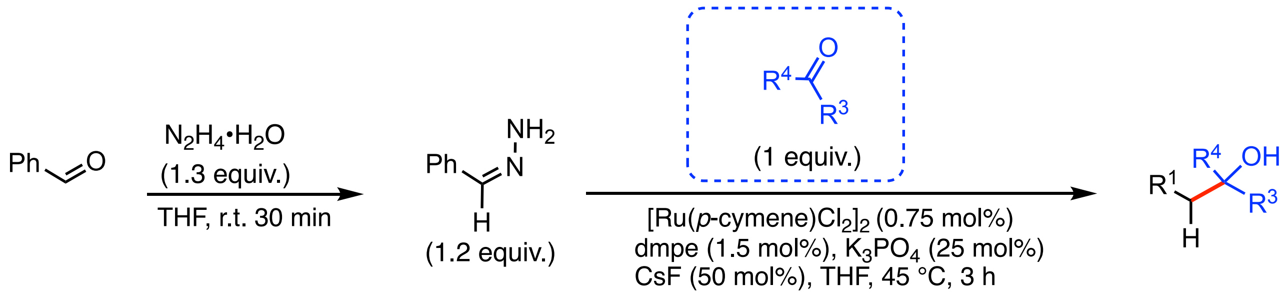
70%

heterocyclic ketones

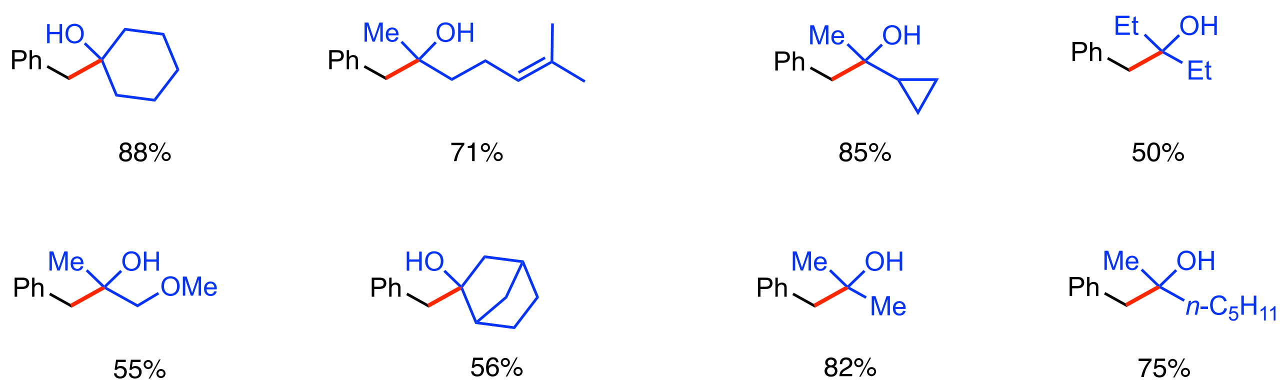


80%

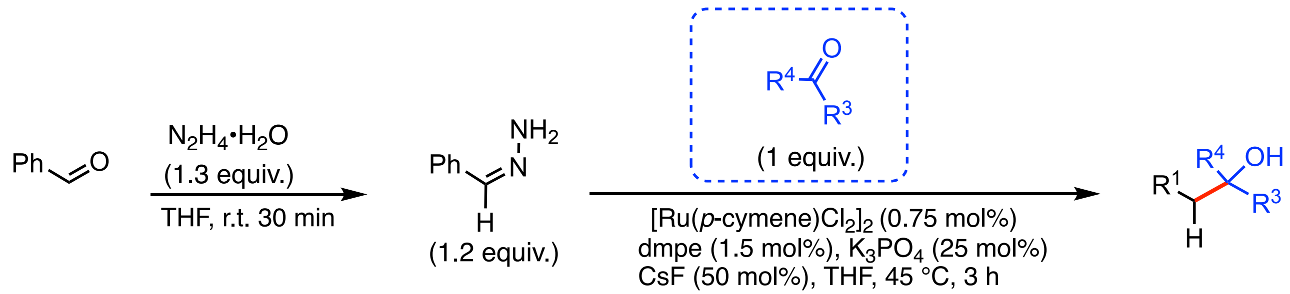
Substrate Scope: Electrophilic Carbonyl



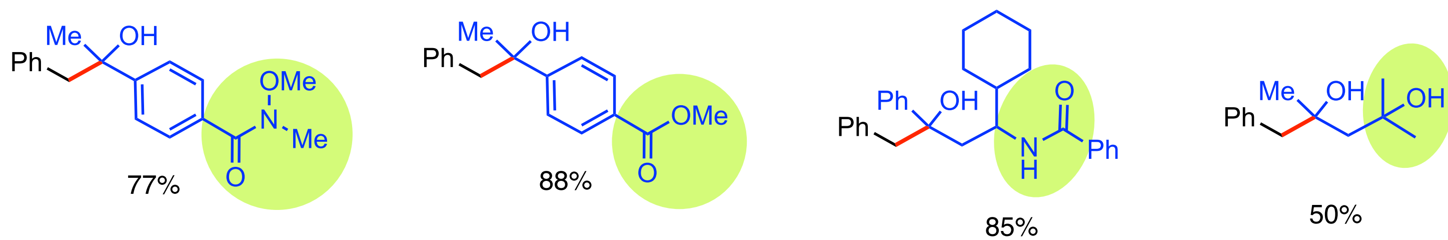
aliphatic ketones



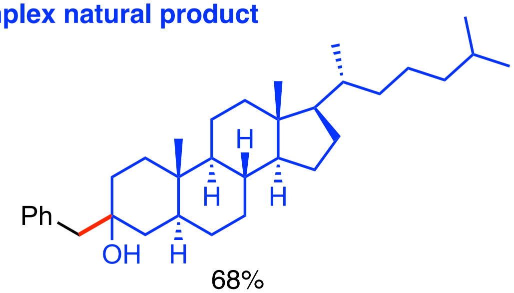
Substrate Scope: Electrophilic Carbonyl



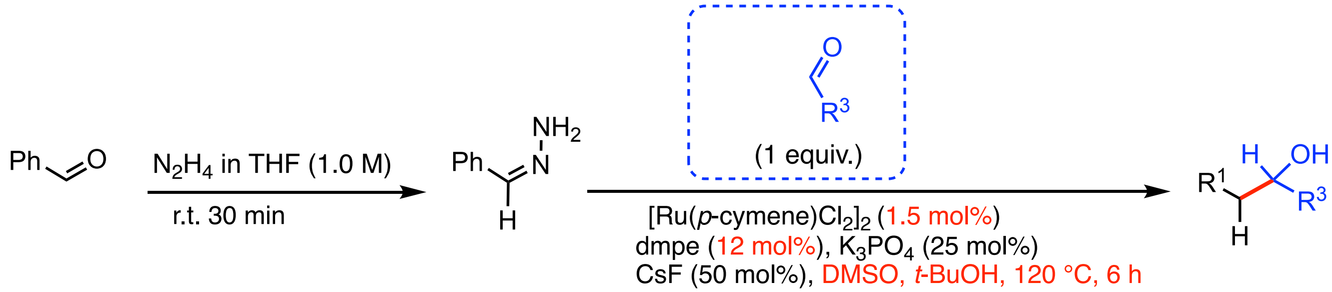
labile functionality tolerated



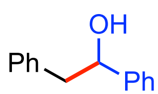
complex natural product



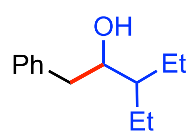
Substrate Scope: Electrophilic Carbonyl



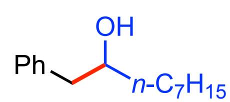
aromatic/aliphatic aldehydes



48%

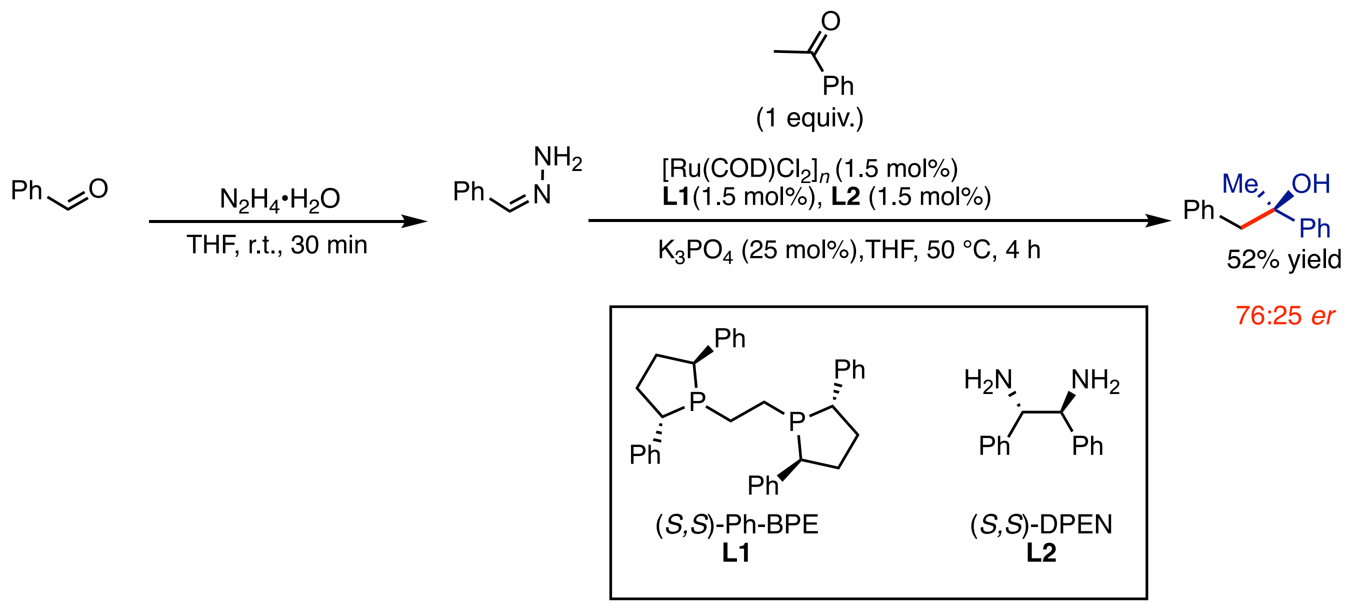


61%

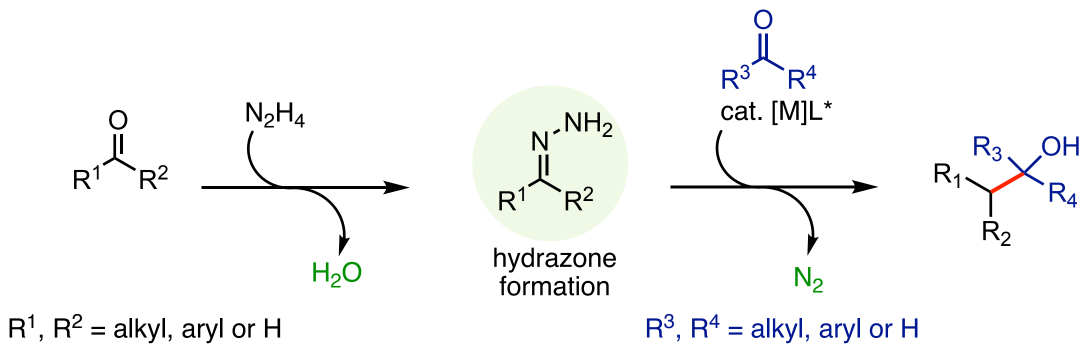


50%

Asymmetric Variant



Conclusions



- Hydrazones act as carbanion equivalents for Ru-catalyzed carbonyl 1,2-additions to aldehydes and ketones to yield 2° and 3° alcohols
- Green alternative to classic methods that utilize stoichiometric organometallic reagents
- Hydrazones can be derived from naturally-occurring aldehydes and ketones
- Excellent chemoselectivity
- Broad functional group tolerance
- Reaction scope largely features at least one aromatic carbonyl partner
- Reaction moderately enantioselective