Catalytic Transfer Functionalization through Shuttle Catalysis

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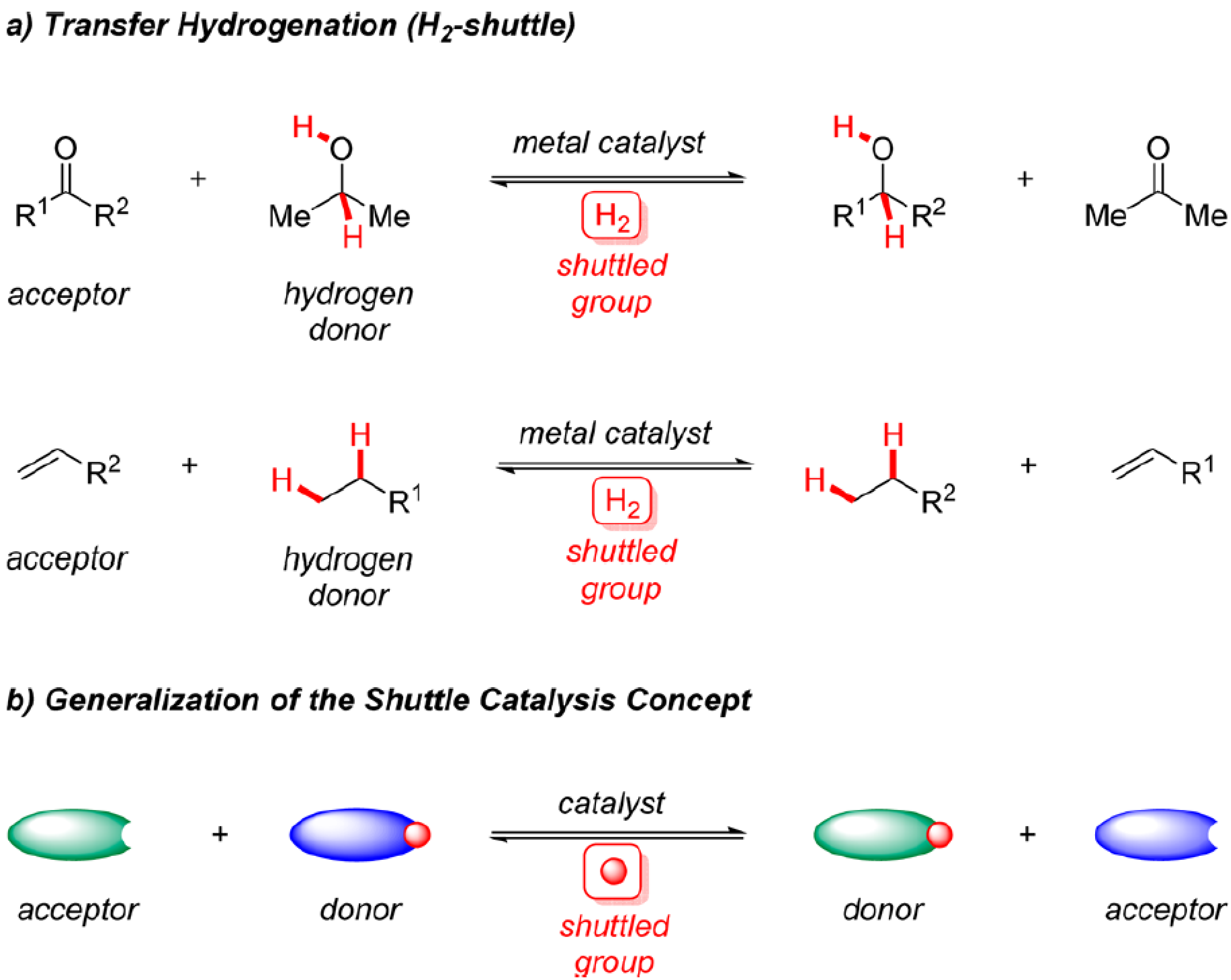
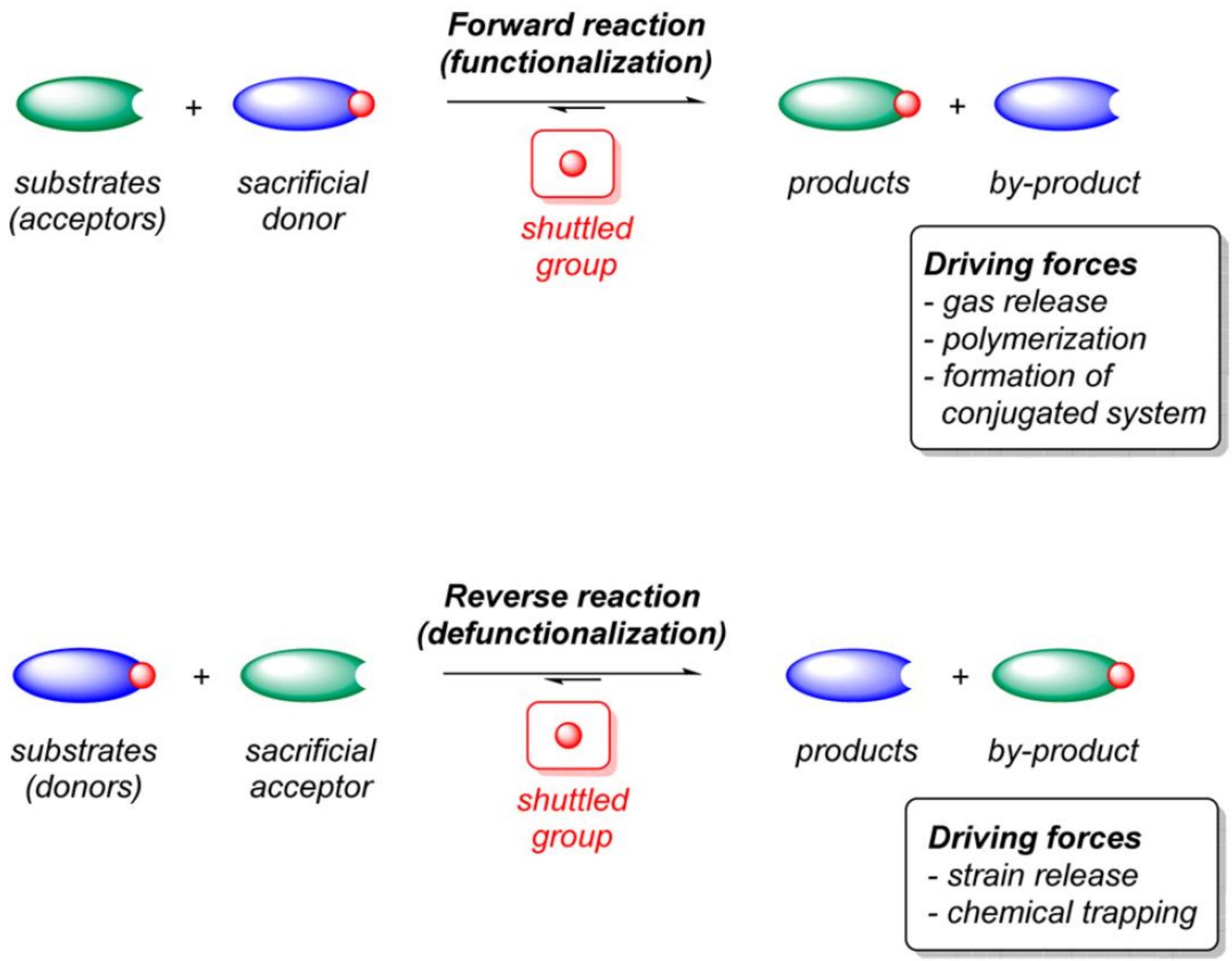
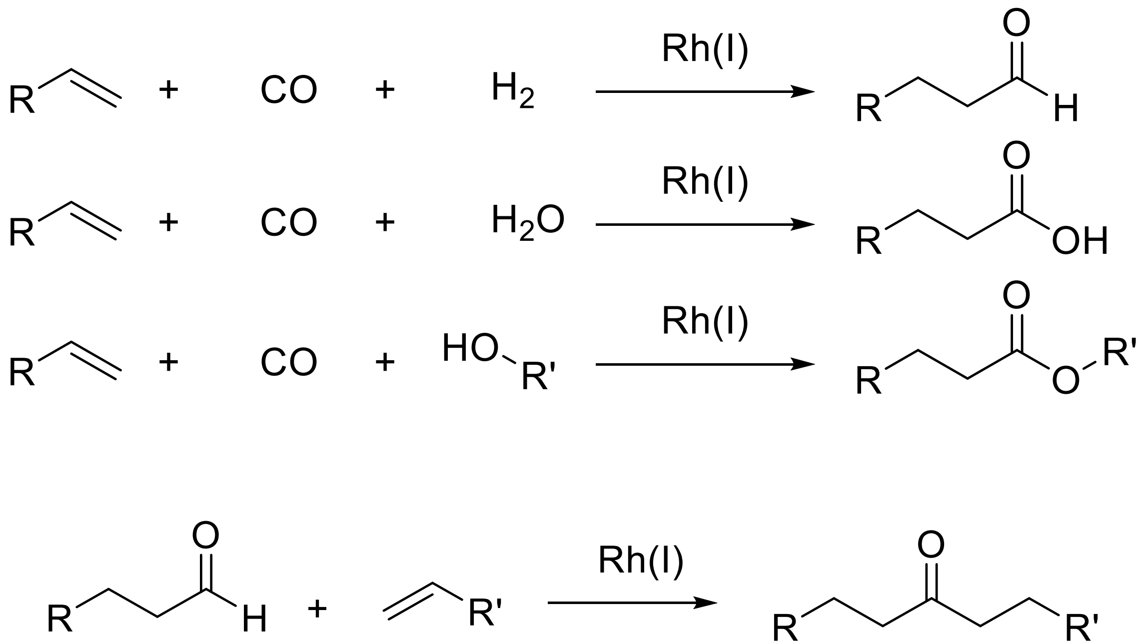
Morandi. B., *et al.* *ACS Catal.* **2016**, *6*, 7528
Morandi. B., *et al. Chem. Eur. J.* **2017**, DIO: 10.1002/chem.201605325

1. Introduction

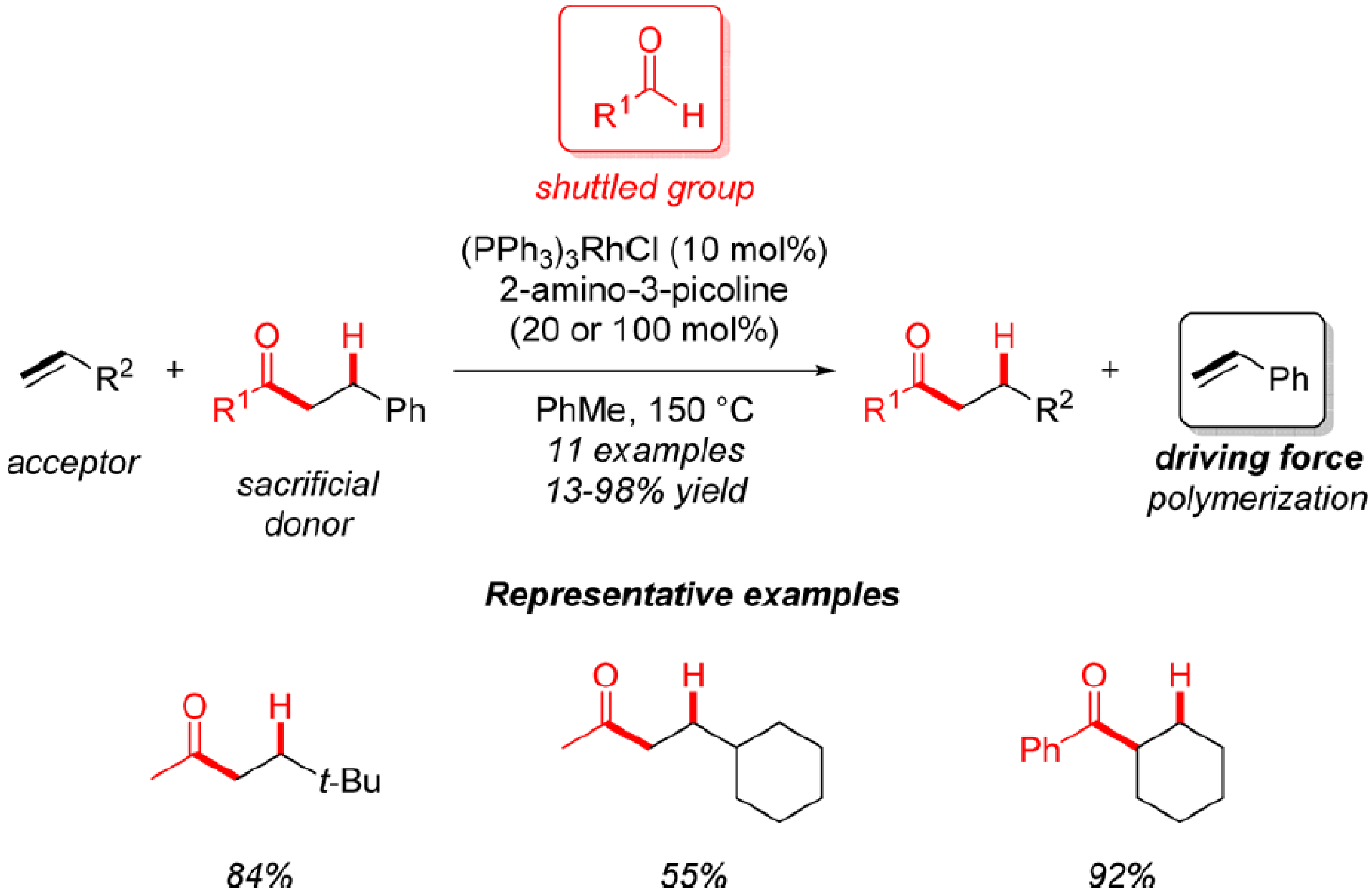



Forward reaction
(functionalization)
+
+
substrates
(acceptors)
sacrificial
donor
shuttled
group
products
by-product
Driving forces
- gas release
- polymerization
- formation of
conjugated system
Reverse reaction
(defunctionalization)
+
+
substrates
(donors)
sacrificial
acceptor
shuttled
group
products
by-product
Driving forces
- strain release
- chemical trapping



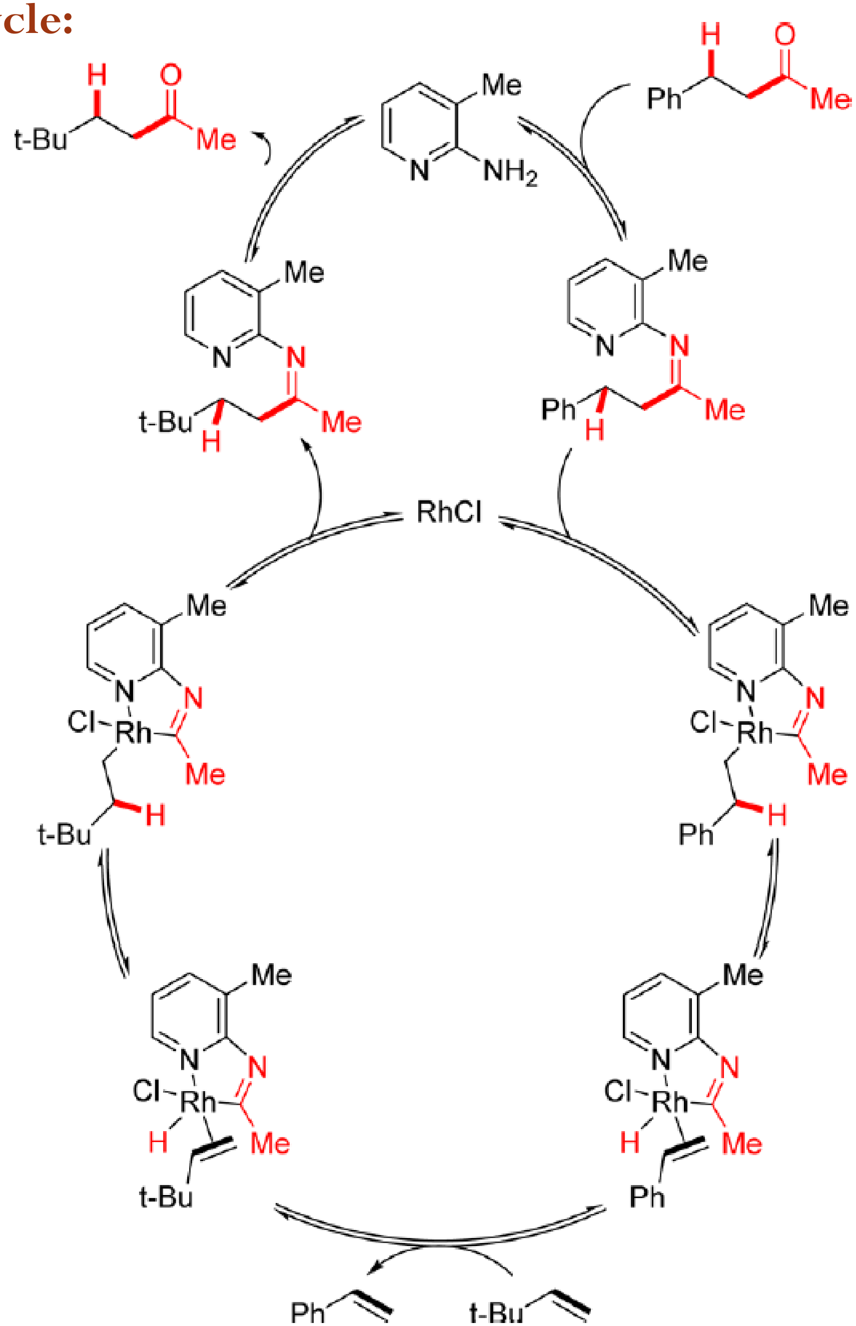
Willis, M. C. *Chem. Rev.* **2010**, *110*, 725

2. Seminal examples of shuttle catalysis beyond hydrogen transfer:

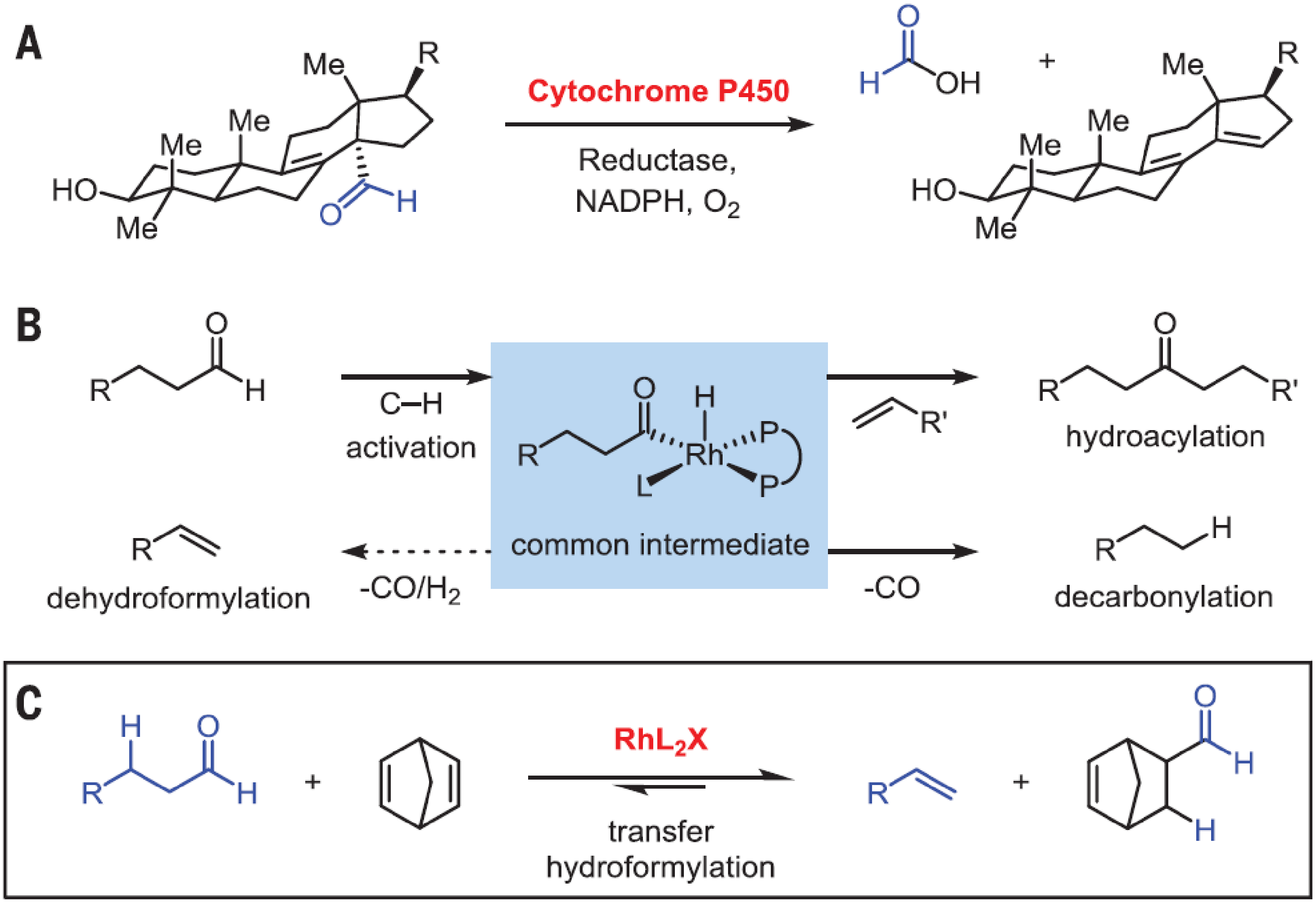


Jun, C.-H., *et al. J. Am. Chem. Soc.* **1999**, *121*, 880

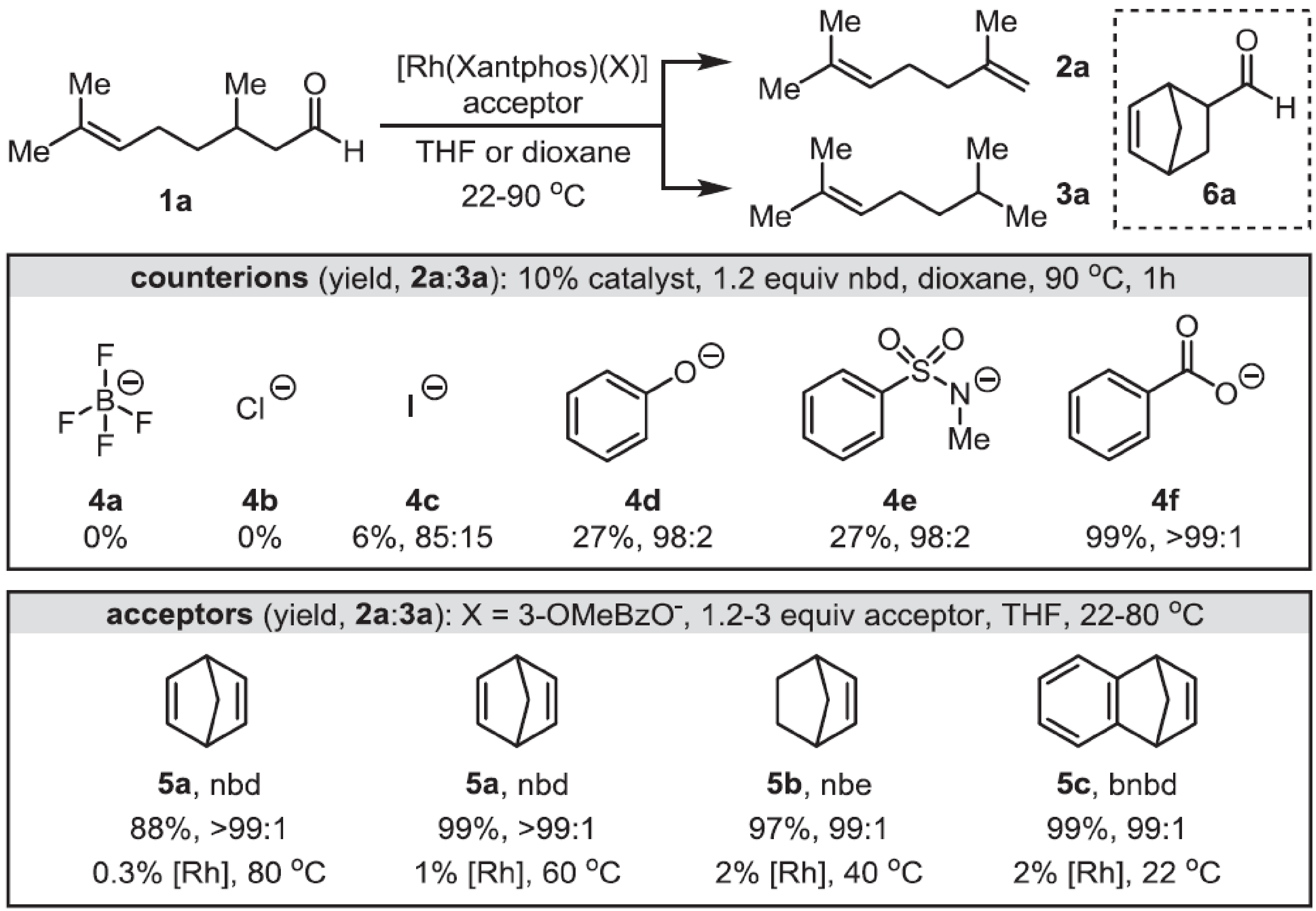
Proposed catalytic cycle:

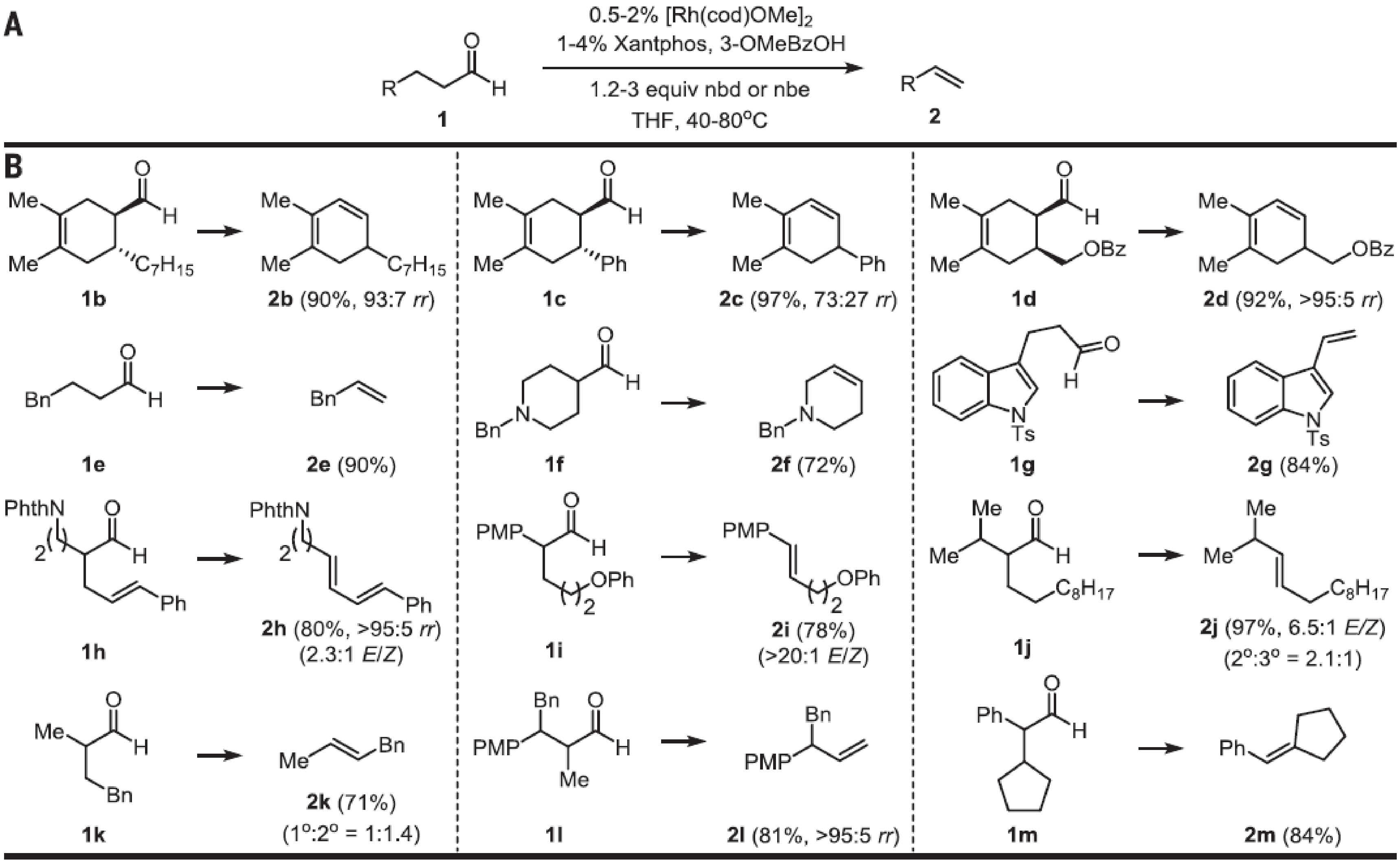


3. Rhodium catalyzed retro-hydroformylation:

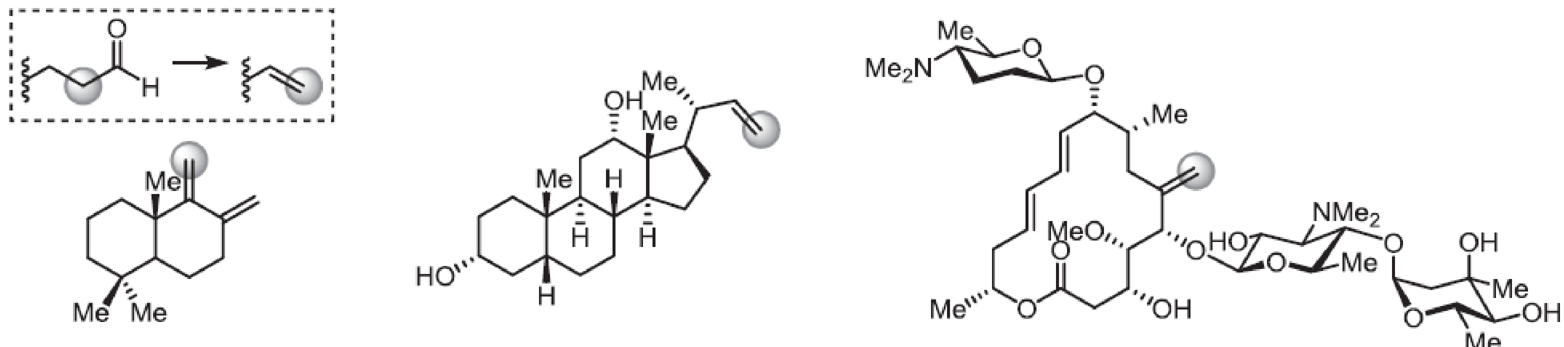


Dong, V. M, *et al.* *Science* **2015**, *347*, 56


[Rh(Xantphos)(X)]
acceptor
THF or dioxane
22-90 °C
1a
2a
3a
6a
counterions (yield, 2a:3a): 10% catalyst, 1.2 equiv nbd, dioxane, 90 °C, 1h
4a
0%
4b
0%
4c
6%, 85:15
4d
27%, 98:2
4e
27%, 98:2
4f
99%, >99:1
acceptors (yield, 2a:3a): X = 3-OMeBzO⁻, 1.2-3 equiv acceptor, THF, 22-80 °C
5a, nbd
88%, >99:1
0.3% [Rh], 80 °C
5a, nbd
99%, >99:1
1% [Rh], 60 °C
5b, nbe
97%, 99:1
2% [Rh], 40 °C
5c, bnbd
99%, 99:1
2% [Rh], 22 °C

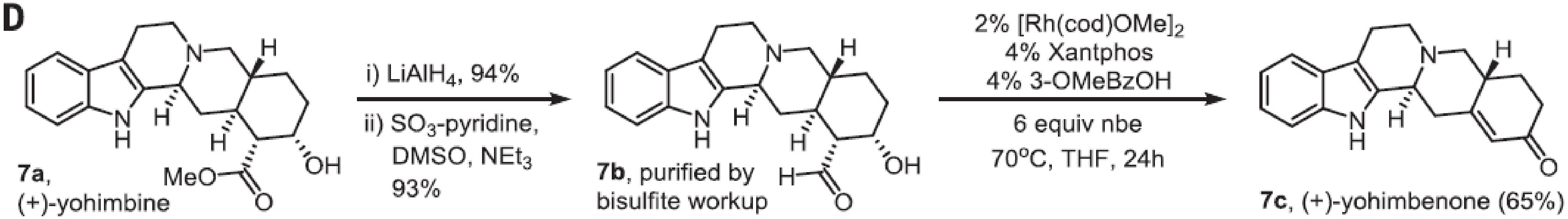

A
0.5-2% [Rh(cod)OMe]2
1-4% Xantphos, 3-OMeBzOH
1.2-3 equiv nbd or nbe
THF, 40-80°C
1
2
B
1b
2b (90%, 93:7 rr)
1c
2c (97%, 73:27 rr)
1d
2d (92%, >95:5 rr)
1e
2e (90%)
1f
2f (72%)
1g
2g (84%)
1h
2h (80%, >95:5 rr)
(2.3:1 E/Z)
1i
2i (78%)
(>20:1 E/Z)
1j
2j (97%, 6.5:1 E/Z)
(2°:3° = 2.1:1)
1k
2k (71%)
(1°:2° = 1:1.4)
1l
2l (81%, >95:5 rr)
1m
2m (84%)

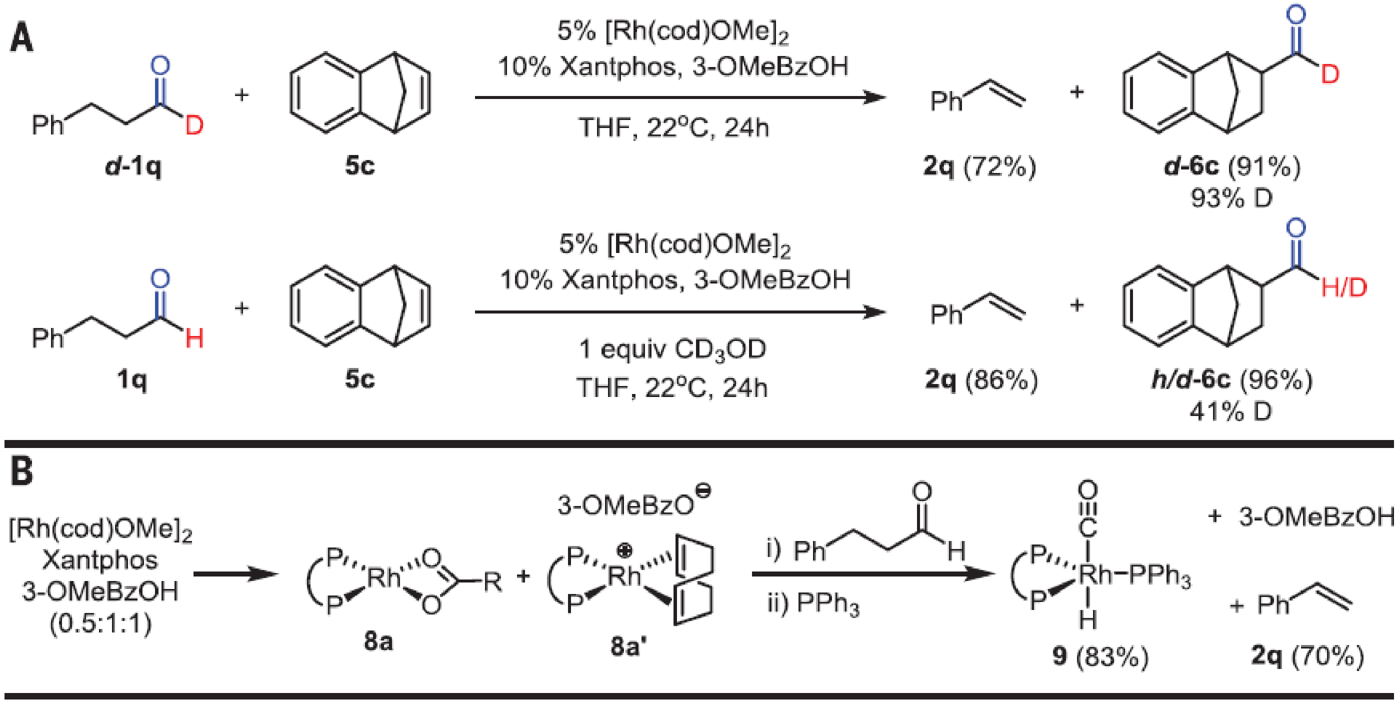
C

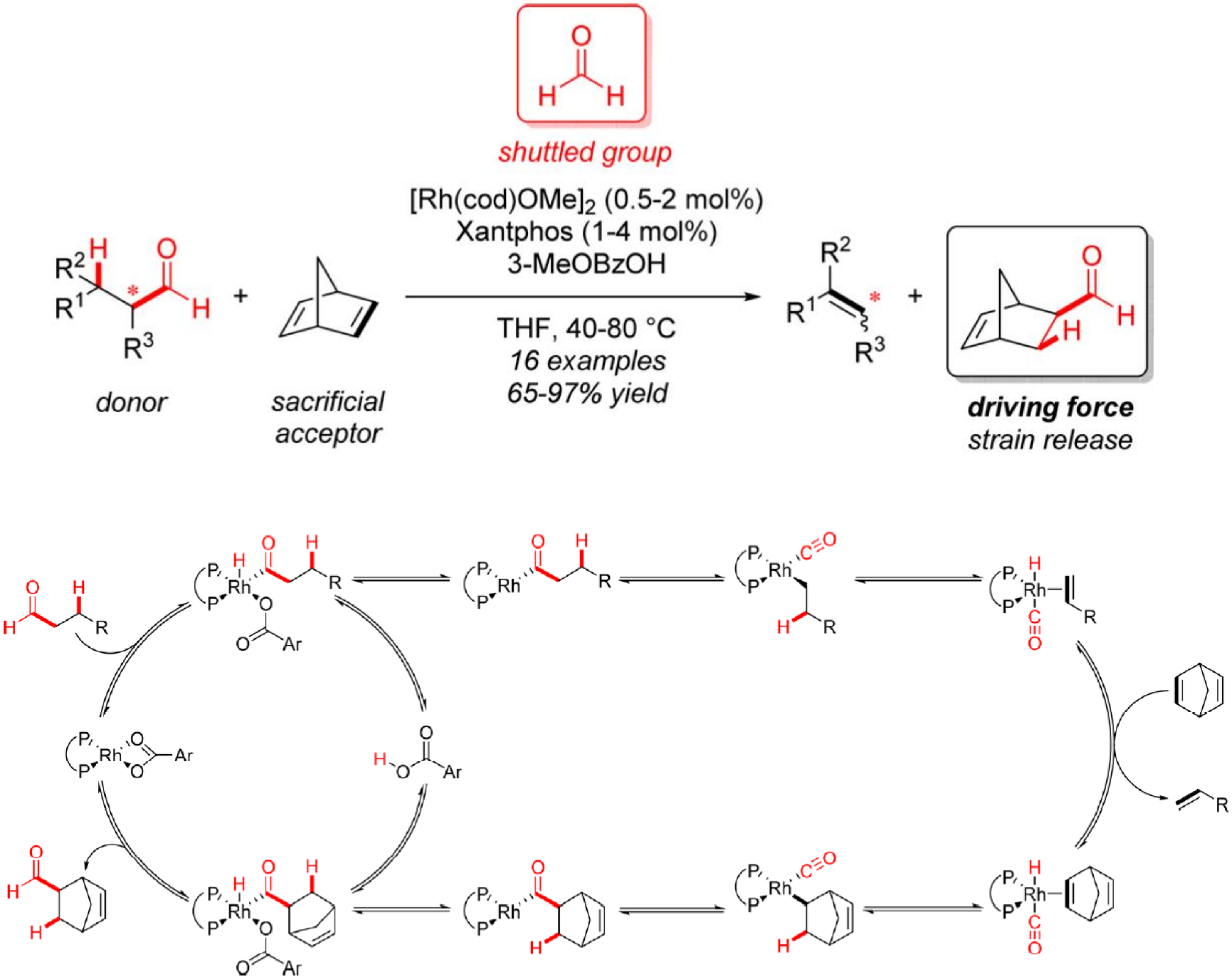


2n (82%) **2o** (68%) **2p** (78%)

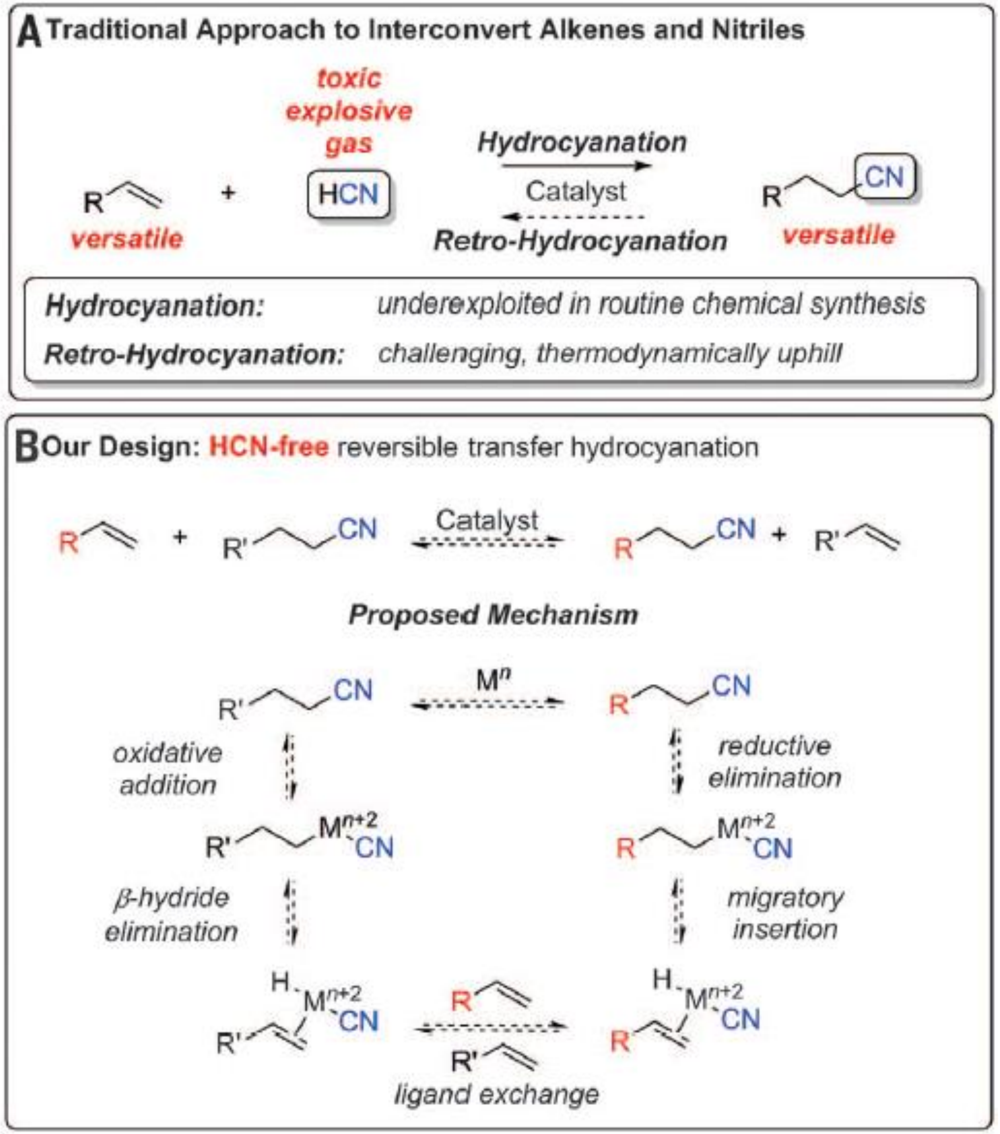
D




A
Ph
d-1q
5c
5% [Rh(cod)OMe]2
10% Xantphos, 3-OMeBzOH
THF, 22°C, 24h
2q (72%)
d-6c (91%)
93% D
1q
1 equiv CD3OD
2q (86%)
h/d-6c (96%)
41% D
B
[Rh(cod)OMe]2
Xantphos
3-OMeBzOH
(0.5:1:1)
8a
3-OMeBzO
8a'
i) Ph
ii) PPh3
+ 3-OMeBzOH
9 (83%)
2q (70%)

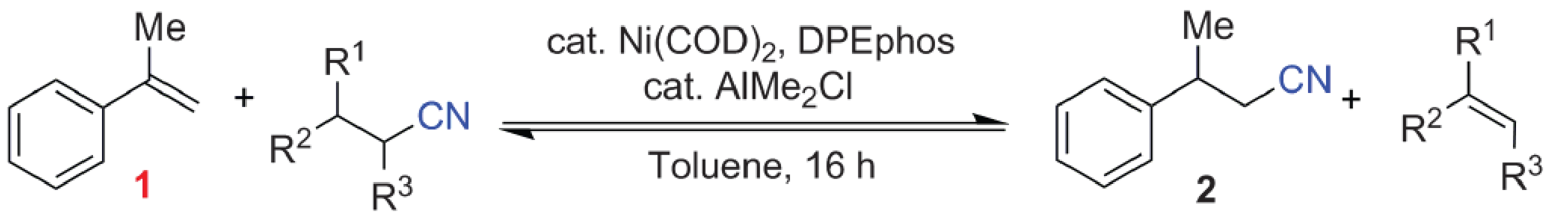

shuttled group
[Rh(cod)OMe]2 (0.5-2 mol%)
Xantphos (1-4 mol%)
3-MeOBzOH
THF, 40-80 °C
16 examples
65-97% yield
donor
sacrificial acceptor
driving force
strain release

4. Nickel-catalyzed transfer hydrocyanation reaction:

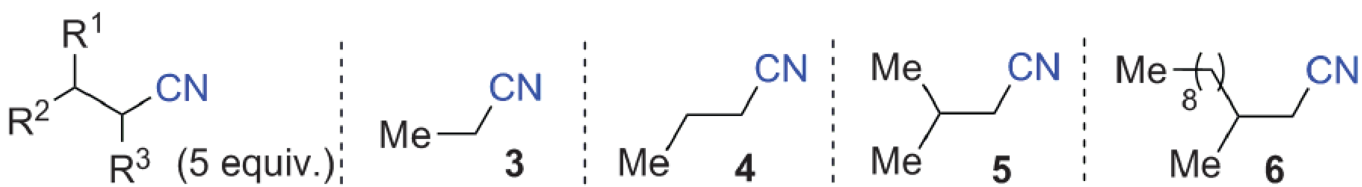


Morandi. B., *et al. Science* **2016**, *351*, 832

A Thermodynamic Challenge: How can we drive the equilibrium to obtain **1** or **2** selectively ?



B Hydrocyanation: Formation of gaseous disubstituted alkene best driving force

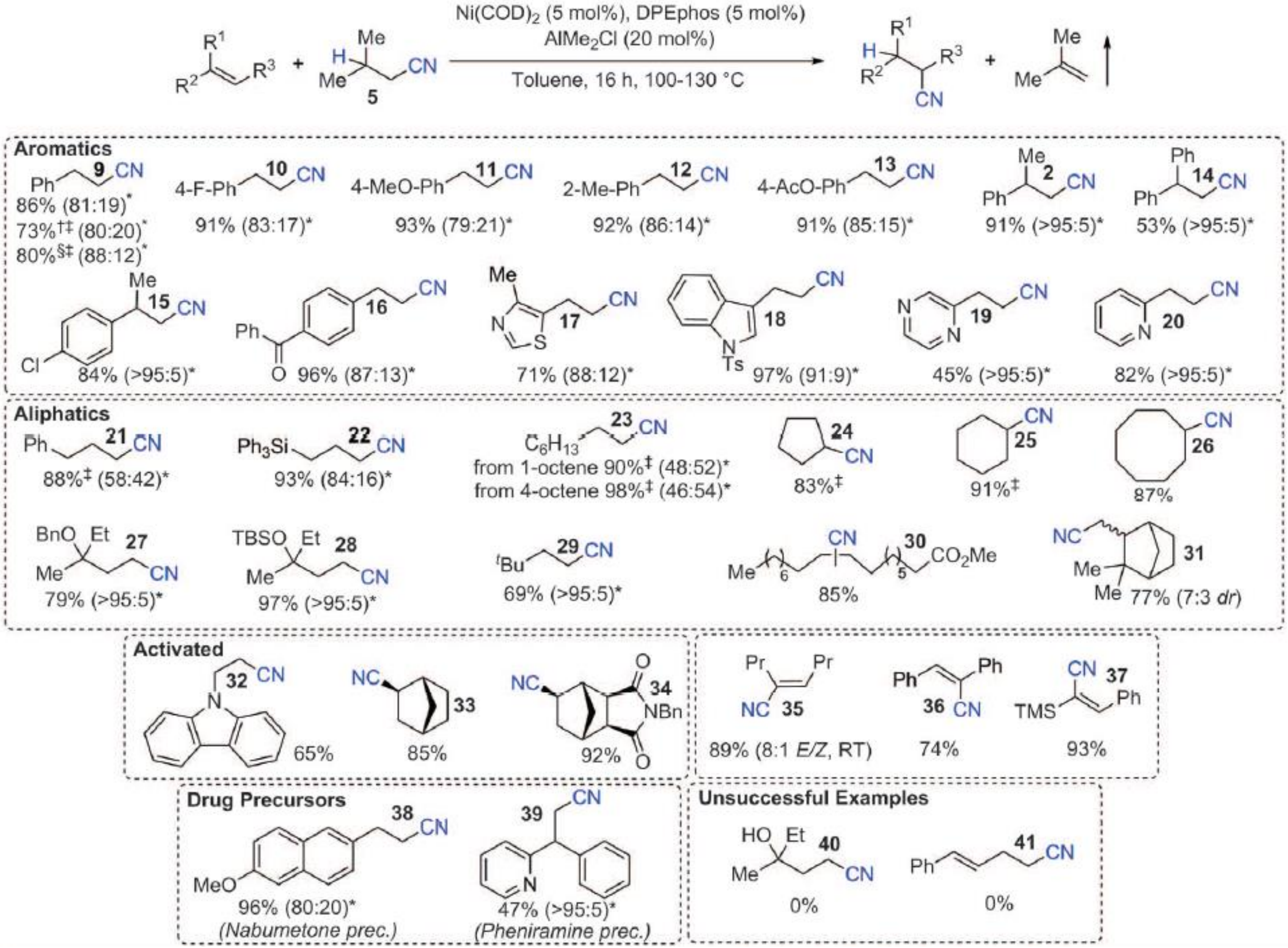


	3	4	5	6
yield **1** -> **2** (100 °C)	3%	26%	69%	60%
open system	—	41%	86%	67%

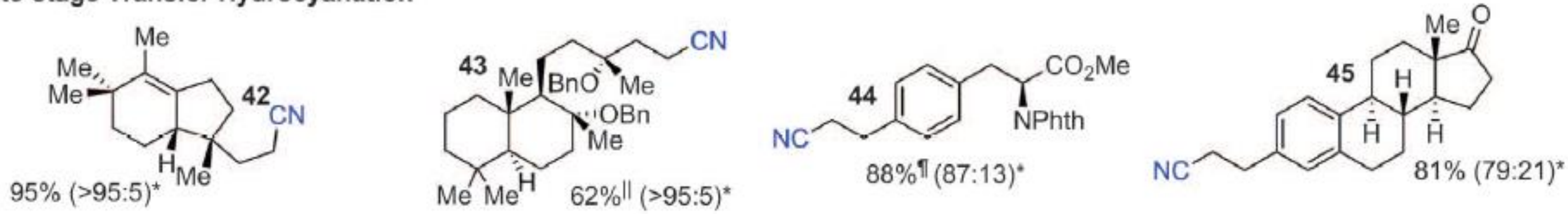
C Retro-Hydrocyanation: Strained alkenes best driving force

	no acceptor	7	8
yield **2** -> **1** (28 °C)	<5%	46%	99%

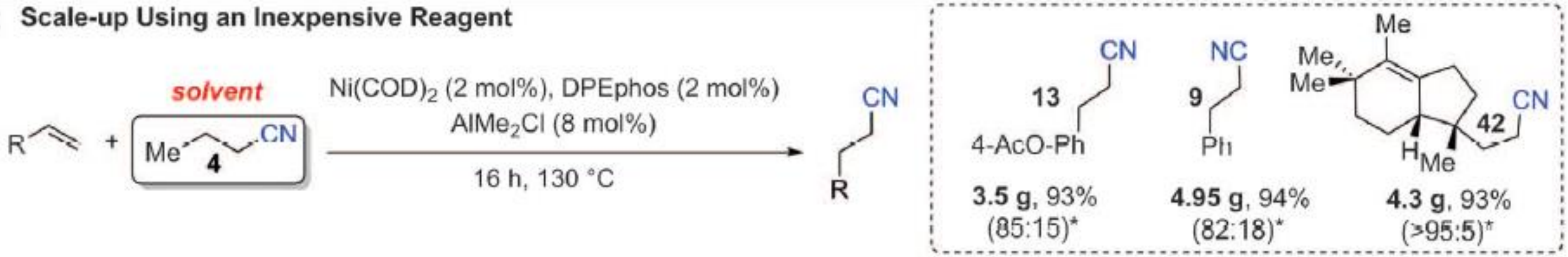
A Scope of the Hydrocyanation

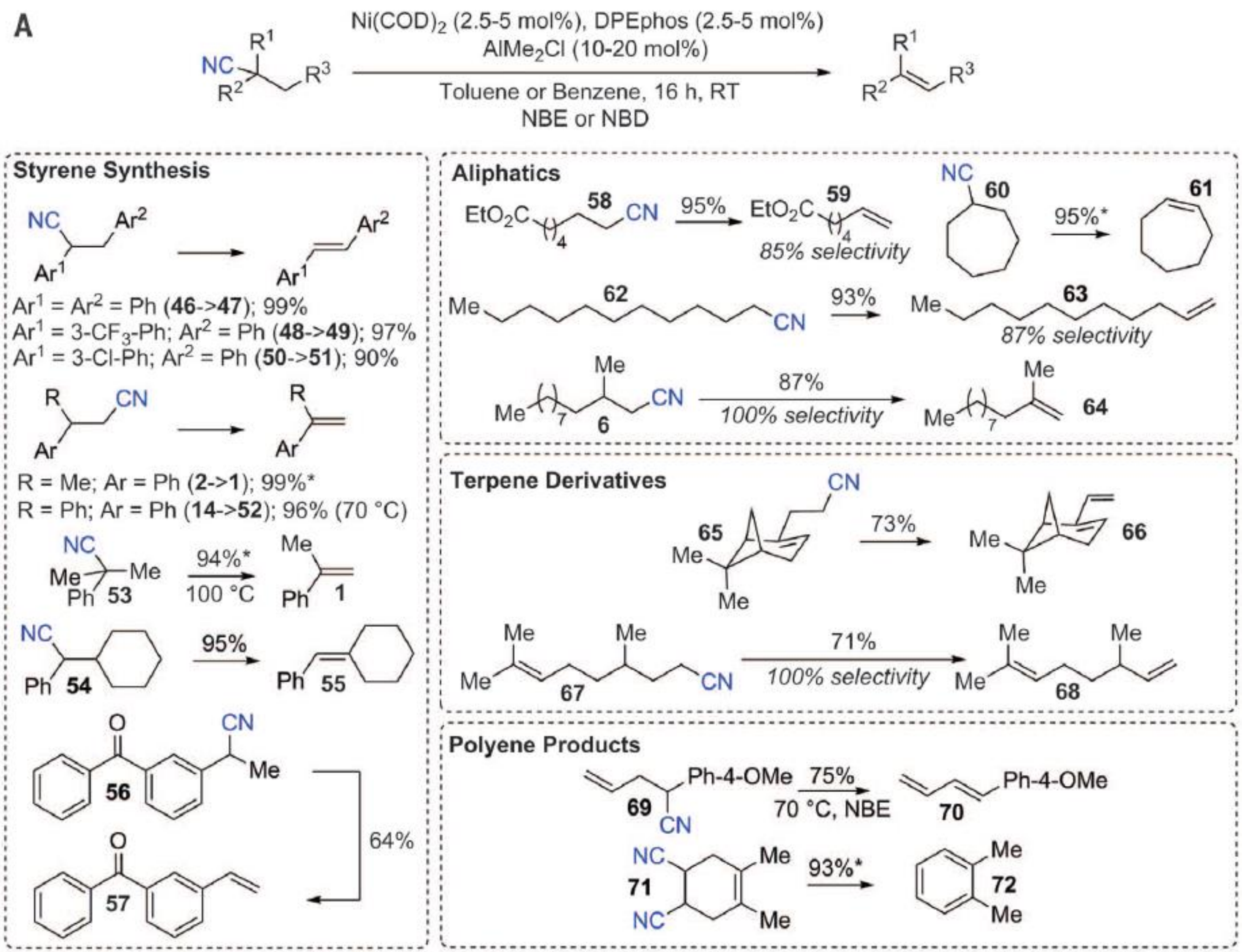


B **Late-stage Transfer Hydrocyanation**

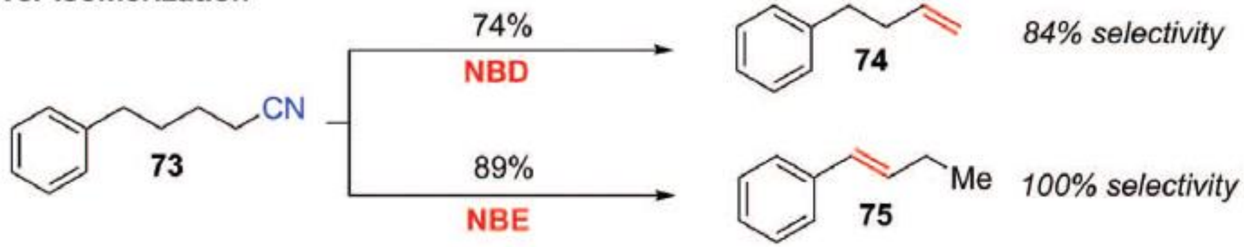


C **Scale-up Using an Inexpensive Reagent**

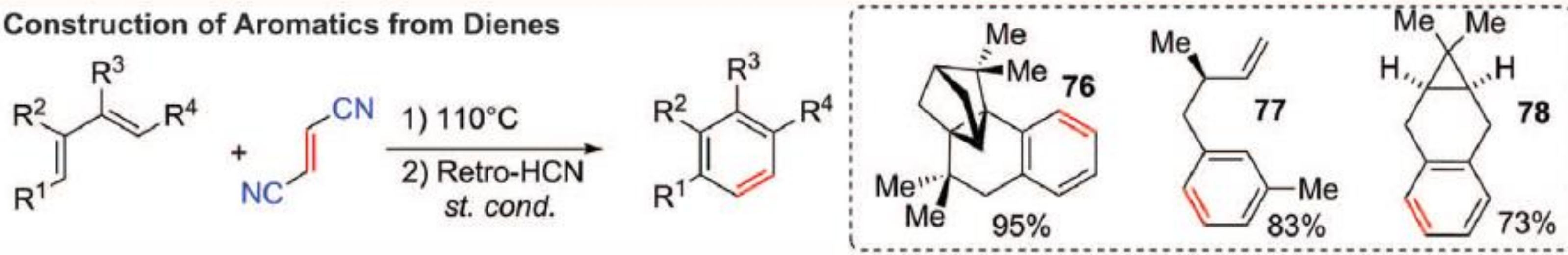



A
Ni(COD)2 (2.5-5 mol%), DPEphos (2.5-5 mol%)
AlMe2Cl (10-20 mol%)
Toluene or Benzene, 16 h, RT
NBE or NBD
Styrene Synthesis
Ar1 = Ar2 = Ph (46->47); 99%
Ar1 = 3-CF3-Ph; Ar2 = Ph (48->49); 97%
Ar1 = 3-Cl-Ph; Ar2 = Ph (50->51); 90%
R = Me; Ar = Ph (2->1); 99%*
R = Ph; Ar = Ph (14->52); 96% (70 °C)
94%*
100 °C
95%
64%
Aliphatics
95%
85% selectivity
95%*
93%
87% selectivity
87%
100% selectivity
Terpene Derivatives
73%
71%
100% selectivity
Polyene Products
75%
70 °C, NBE
93%*

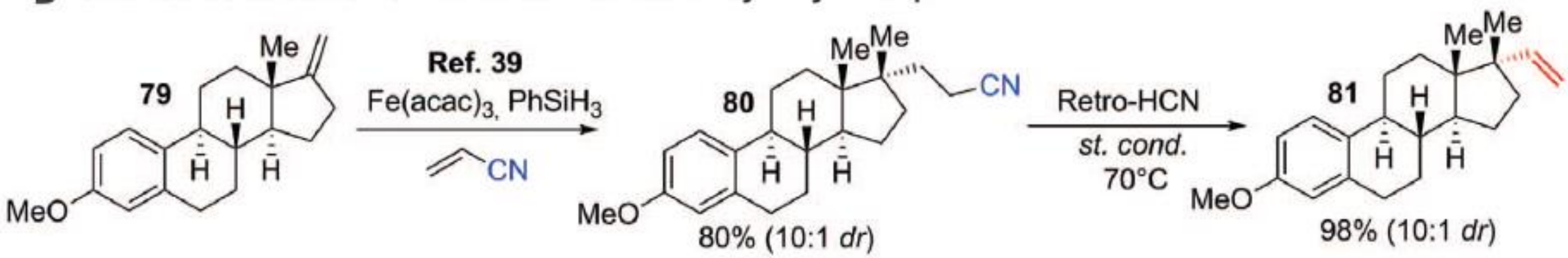
B Control over Isomerization

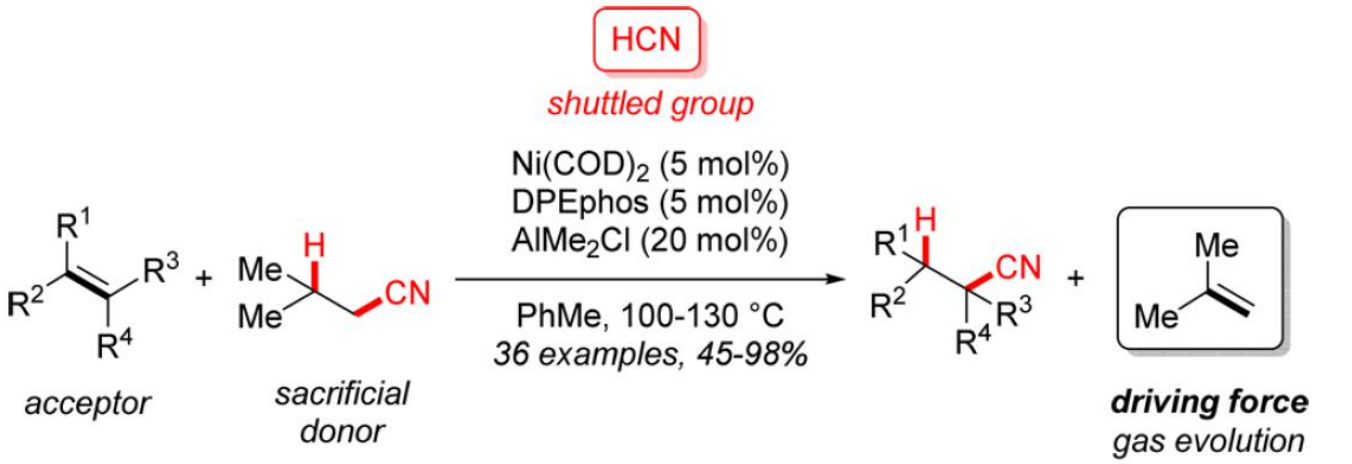


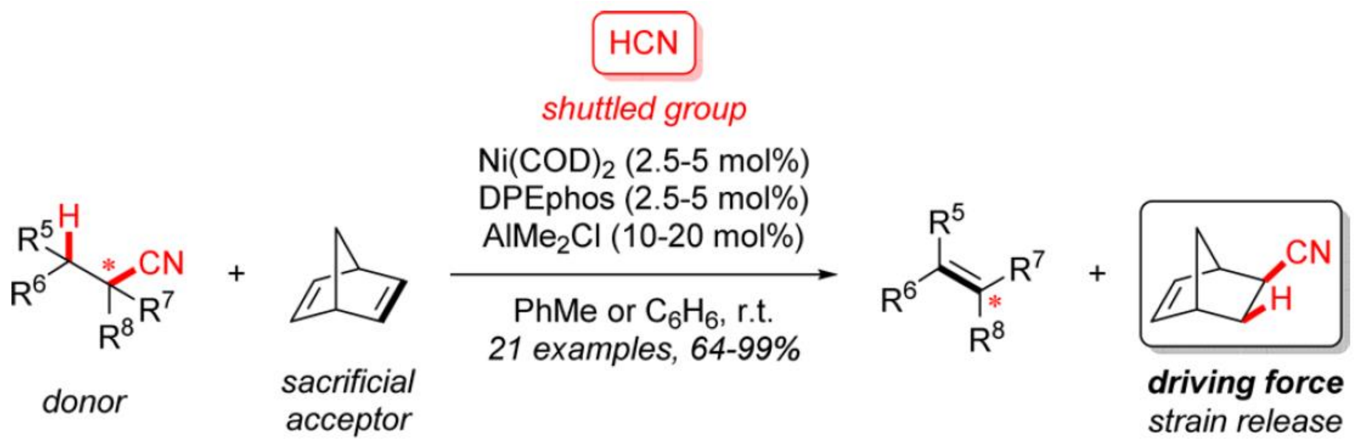
C Construction of Aromatics from Dienes



D Stereoselective Installation of a Chiral Quaternary Vinyl Group

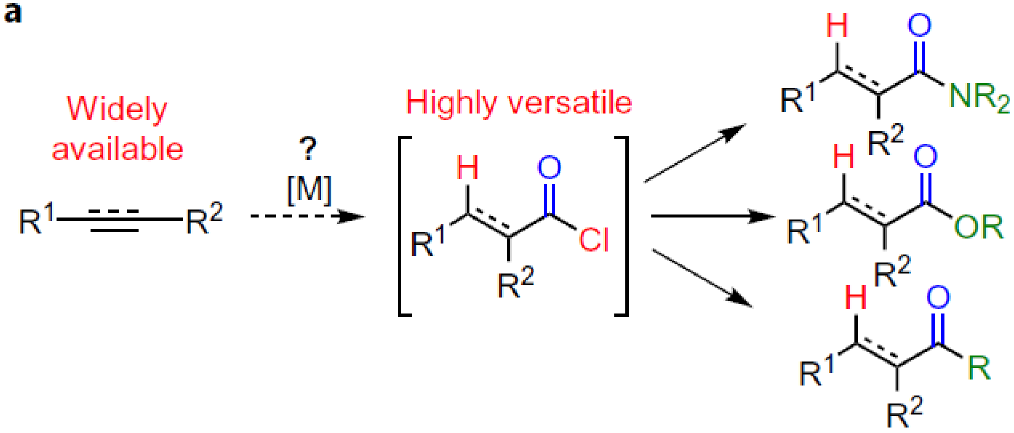



HCN
shuttled group
Ni(COD)2 (5 mol%)
DPEphos (5 mol%)
AlMe2Cl (20 mol%)
PhMe, 100-130 °C
36 examples, 45-98%
acceptor
sacrificial donor
driving force
gas evolution

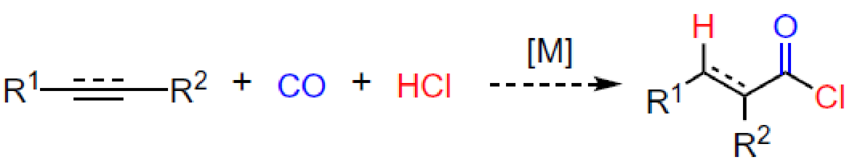

HCN
shuttled group
Ni(COD)2 (2.5-5 mol%)
DPEphos (2.5-5 mol%)
AlMe2Cl (10-20 mol%)
PhMe or C6H6, r.t.
21 examples, 64-99%
donor
sacrificial acceptor
driving force
strain release

5. CO- and HCl-free synthesis of acid chlorides via Palladium catalyzed

a

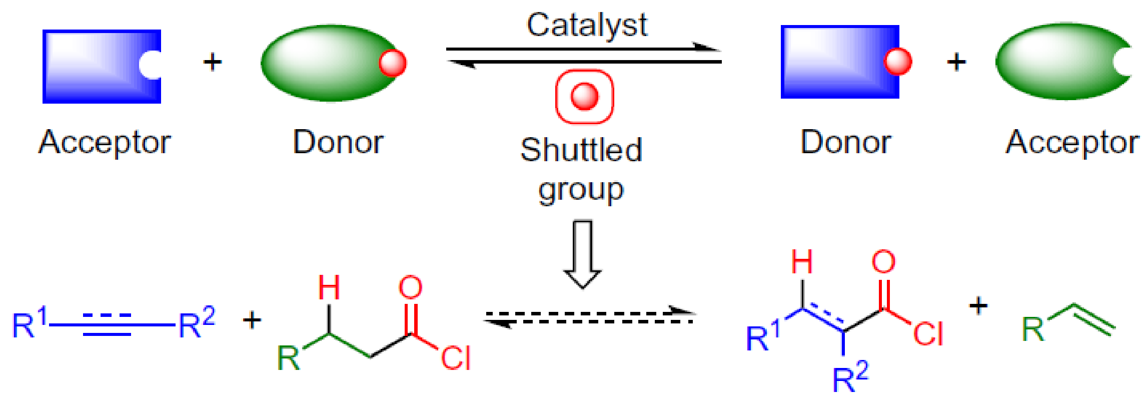


b



Morandi. B., *et al. Nat. Chem.* **2017**, DOI: 10.1038/NCHEM.2798

c


Catalyst
Acceptor
Donor
Shuttled group
Donor
Acceptor
H
O
R1
R2
R
Cl
H
O
R1
Cl
R2
R

d

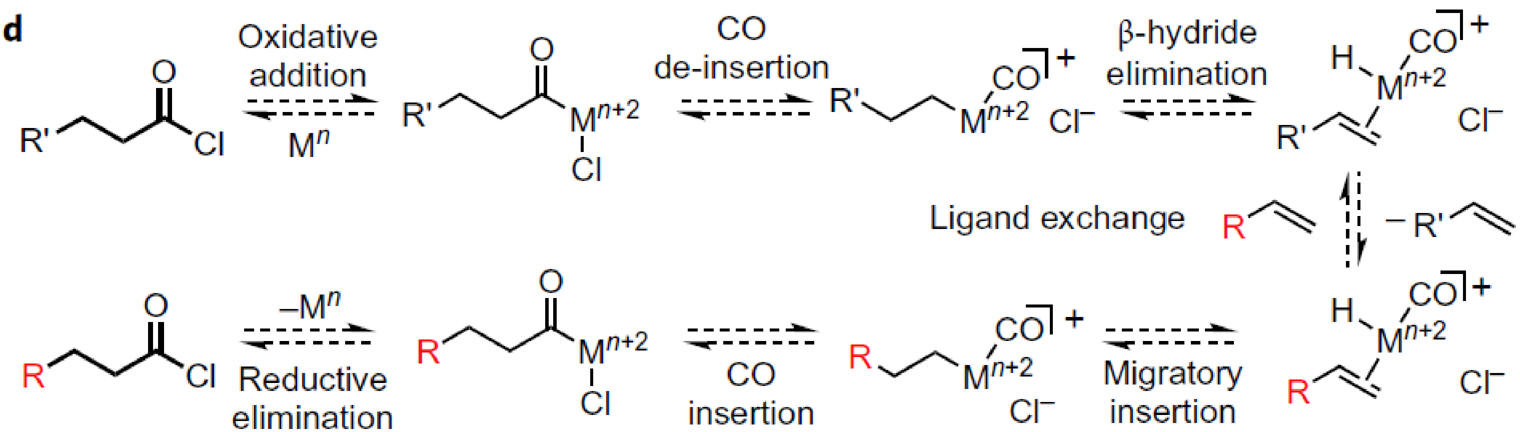
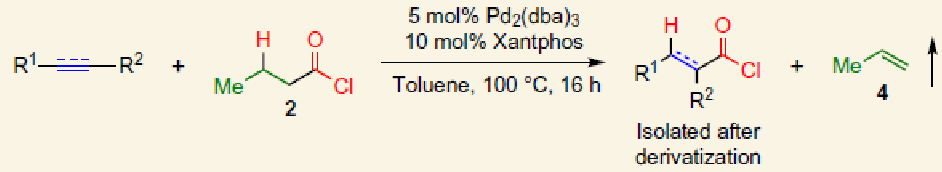

Oxidative addition
Mn
CO de-insertion
β-hydride elimination
Ligand exchange
− R'
–Mn
Reductive elimination
CO insertion
Migratory insertion
R'
O
Cl
Mn+2
CO
Cl−
H
R
+

Table 1 | Scope of the transfer hydrochlorocarbonylation.



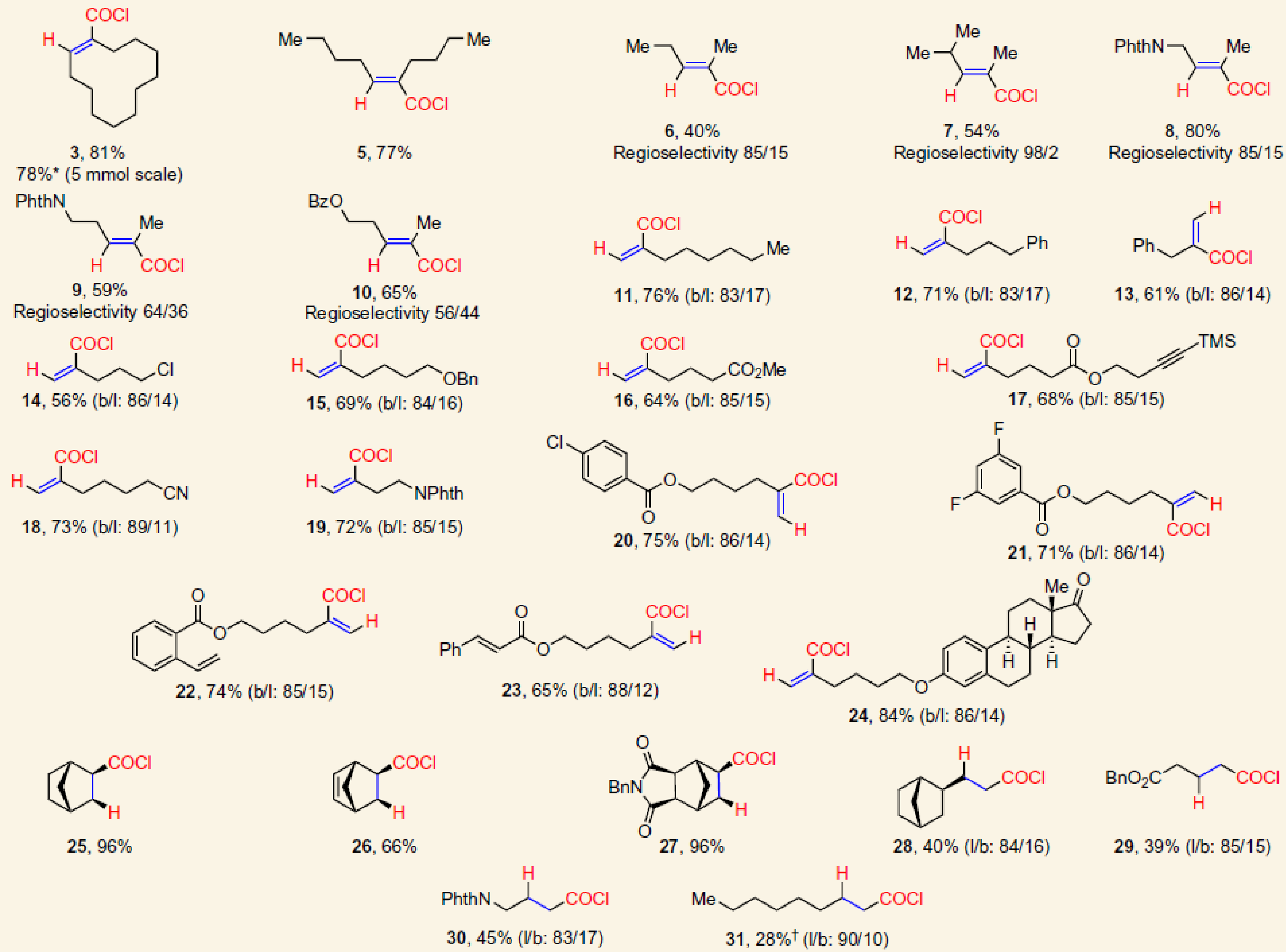
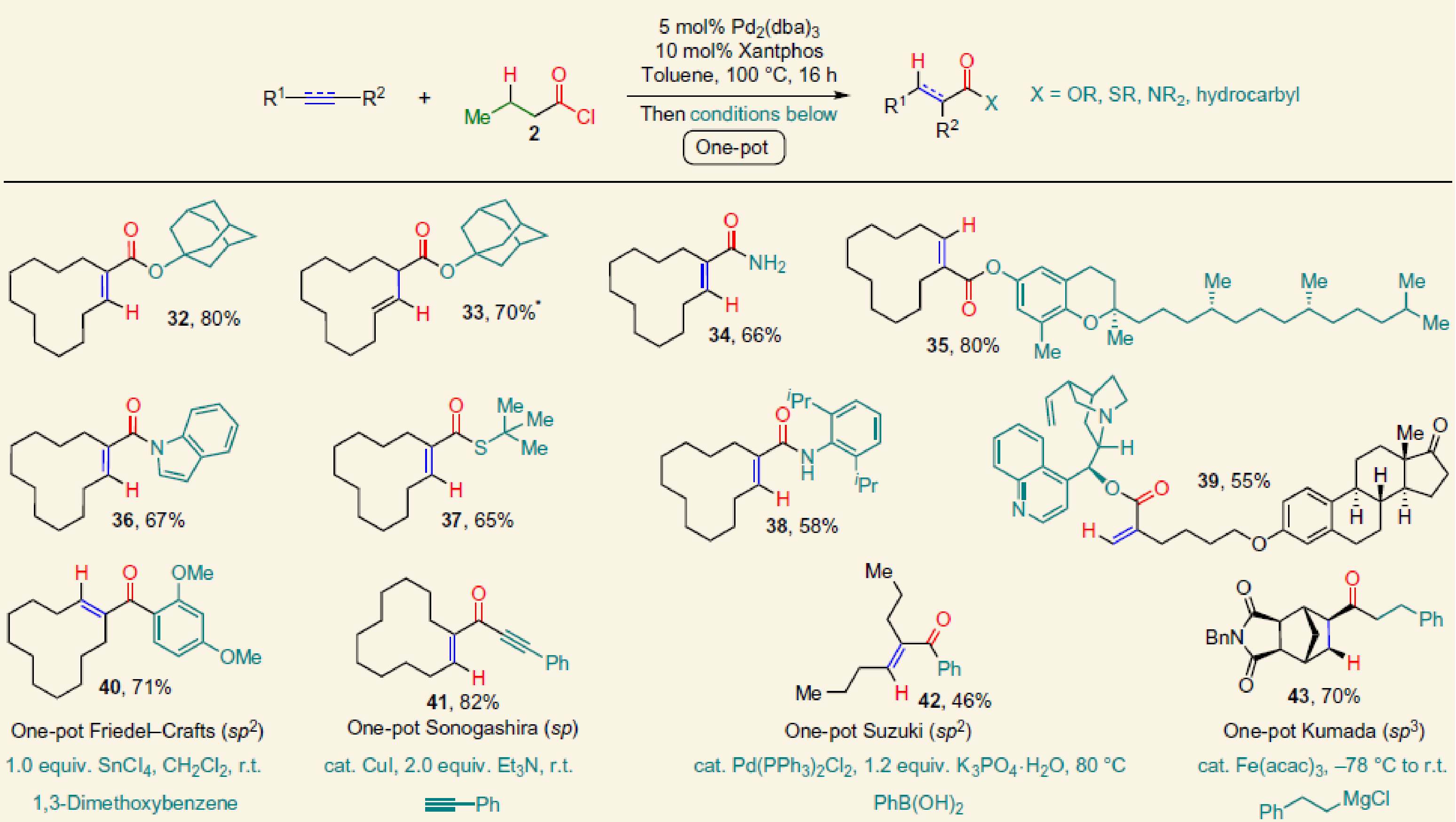
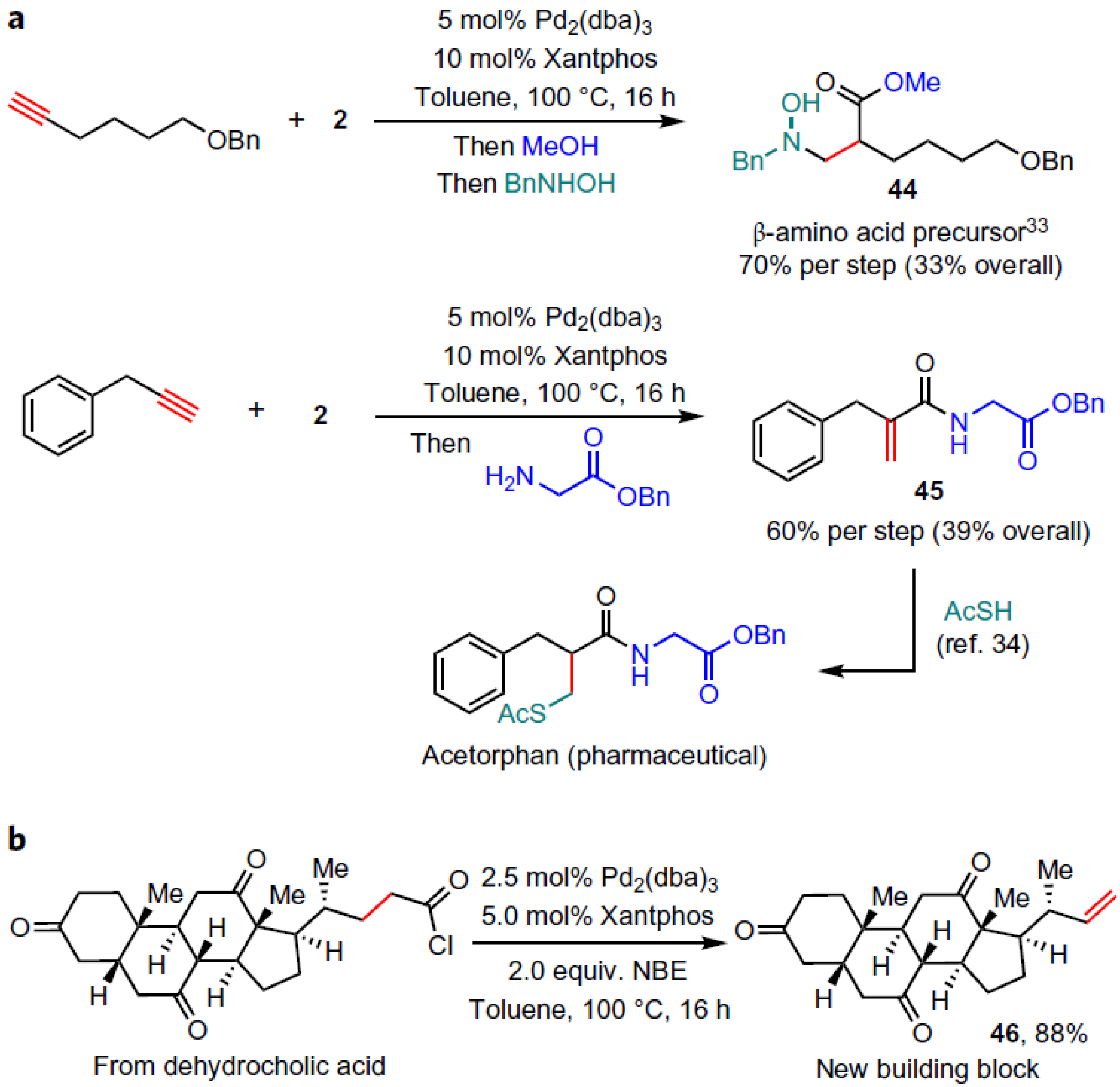
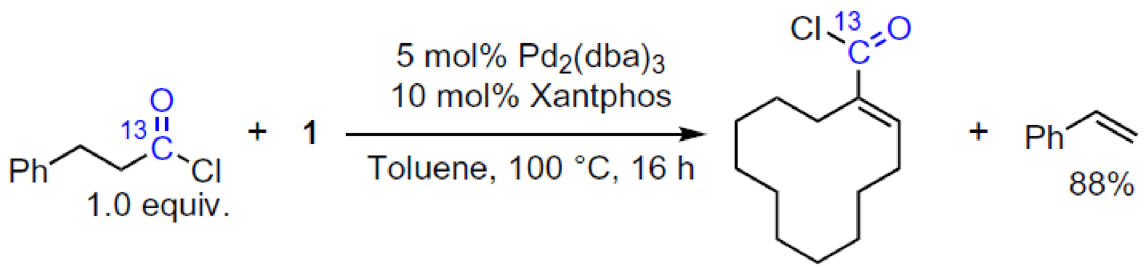


Table 2 | One-pot synthesis of carbonyl-containing products from unsaturated substrates.

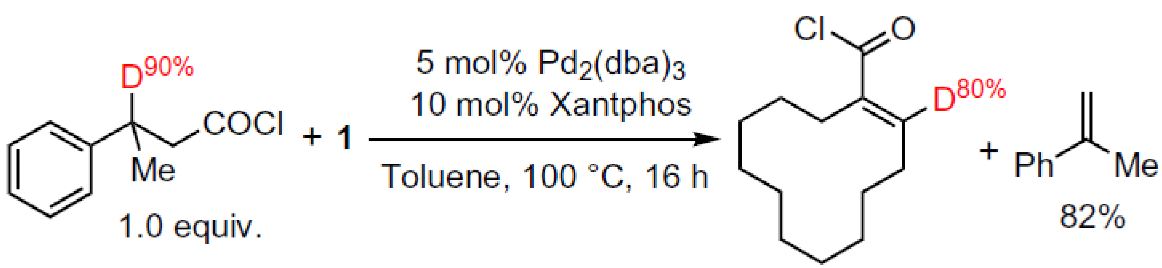


*Base (Et_3N) was added. cat., catalytic; r.t., room temperature.


a
OBn
+ 2
5 mol% Pd2(dba)3
10 mol% Xantphos
Toluene, 100 °C, 16 h
Then MeOH
Then BnNHOH
OH
O
OMe
Bn
N
OBn
44
β-amino acid precursor33
70% per step (33% overall)
+ 2
5 mol% Pd2(dba)3
10 mol% Xantphos
Toluene, 100 °C, 16 h
Then
H2N
O
OBn
O
N
H
OBn
O
45
60% per step (39% overall)
AcSH
(ref. 34)
O
N
H
OBn
O
AcS
Acetorphan (pharmaceutical)
b
O
Me
O
Me
Me
H
H
H
H
H
O
Cl
O
From dehydrocholic acid
2.5 mol% Pd2(dba)3
5.0 mol% Xantphos
2.0 equiv. NBE
Toluene, 100 °C, 16 h
O
Me
O
Me
Me
H
H
H
H
H
O
46, 88%
New building block

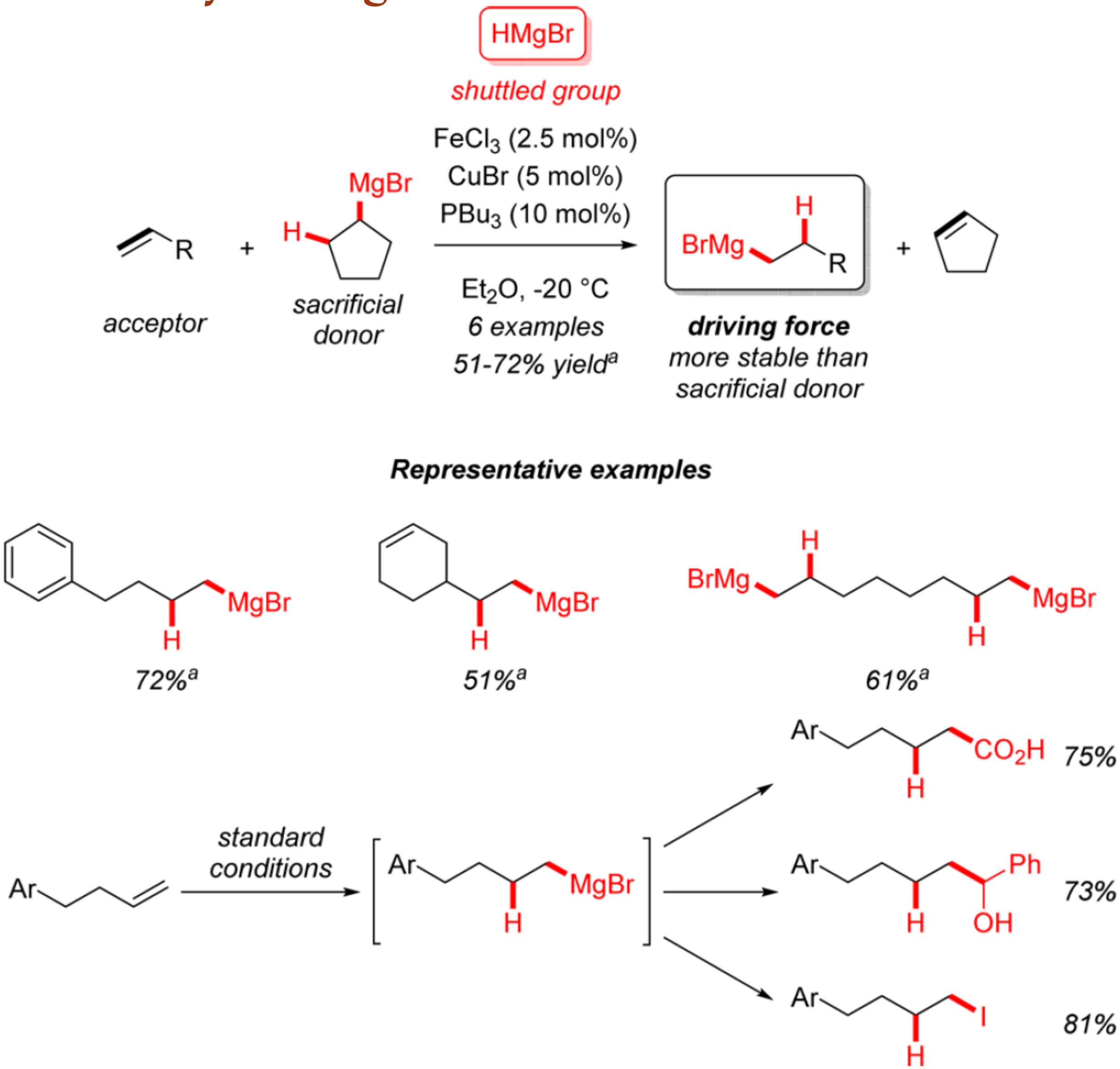

13
O
C
Ph
Cl
1.0 equiv.
+ 1
5 mol% Pd2(dba)3
10 mol% Xantphos
Toluene, 100 °C, 16 h
Cl
13
C
O
+ Ph
88%

47, 75%

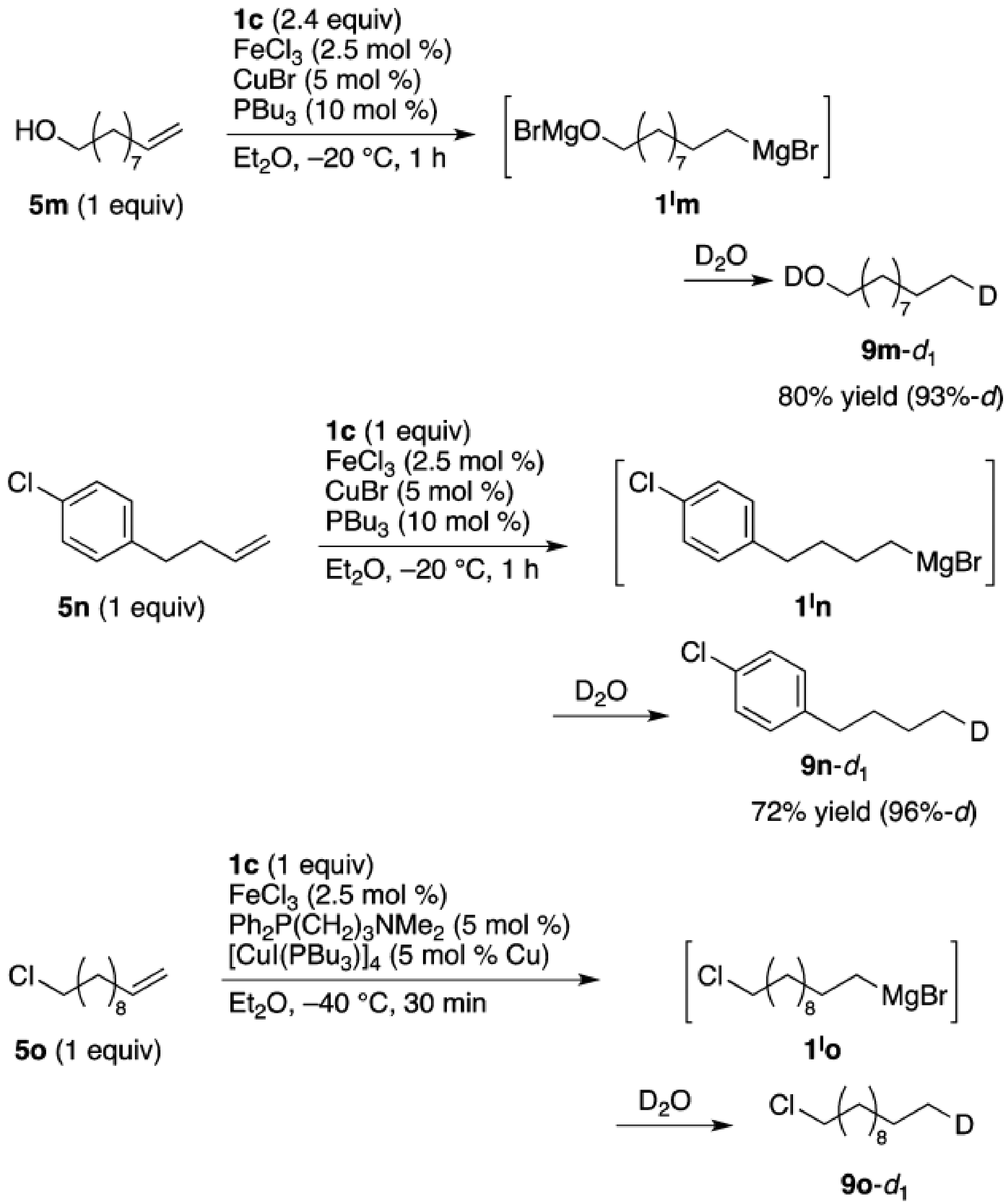

D90%
COCl
Me
1.0 equiv.
+ 1
5 mol% Pd2(dba)3
10 mol% Xantphos
Toluene, 100 °C, 16 h
Cl
O
D80%
+ Ph
Me
82%

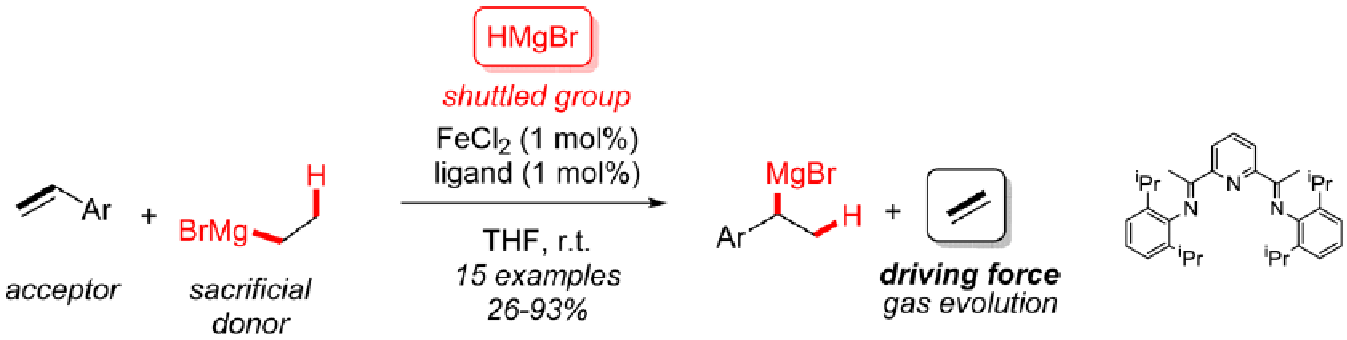
48, 76%

5. Catalytic Transfer Hydromagnesiation:

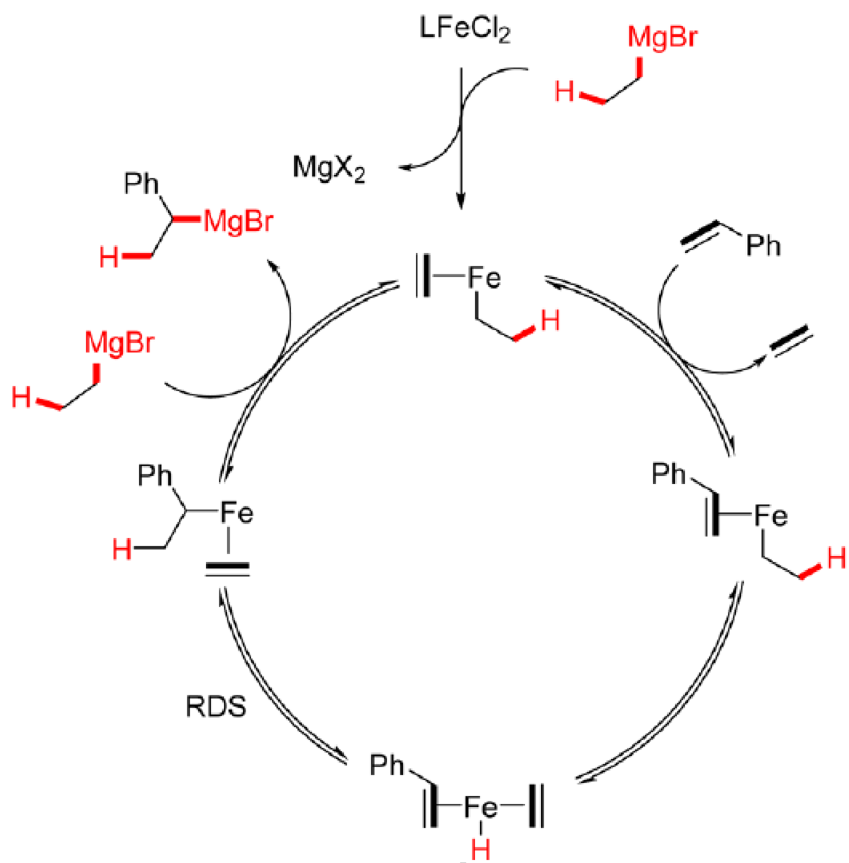


Hayashi, T., *et al.* *J. Am. Chem. Soc.* **2012**, *134*, 272.


1c (2.4 equiv)
FeCl3 (2.5 mol %)
CuBr (5 mol %)
PBu3 (10 mol %)
Et2O, –20 °C, 1 h
HO
7
5m (1 equiv)
BrMgO
MgBr
1'm
D2O
DO
D
9m-d1
80% yield (93%-d)
1c (1 equiv)
FeCl3 (2.5 mol %)
CuBr (5 mol %)
PBu3 (10 mol %)
Et2O, –20 °C, 1 h
Cl
5n (1 equiv)
MgBr
1'n
D2O
D
9n-d1
72% yield (96%-d)
1c (1 equiv)
FeCl3 (2.5 mol %)
Ph2P(CH2)3NMe2 (5 mol %)
[CuI(PBu3)]4 (5 mol % Cu)
Et2O, –40 °C, 30 min
Cl
8
5o (1 equiv)
MgBr
1'o
D2O
D
9o-d1

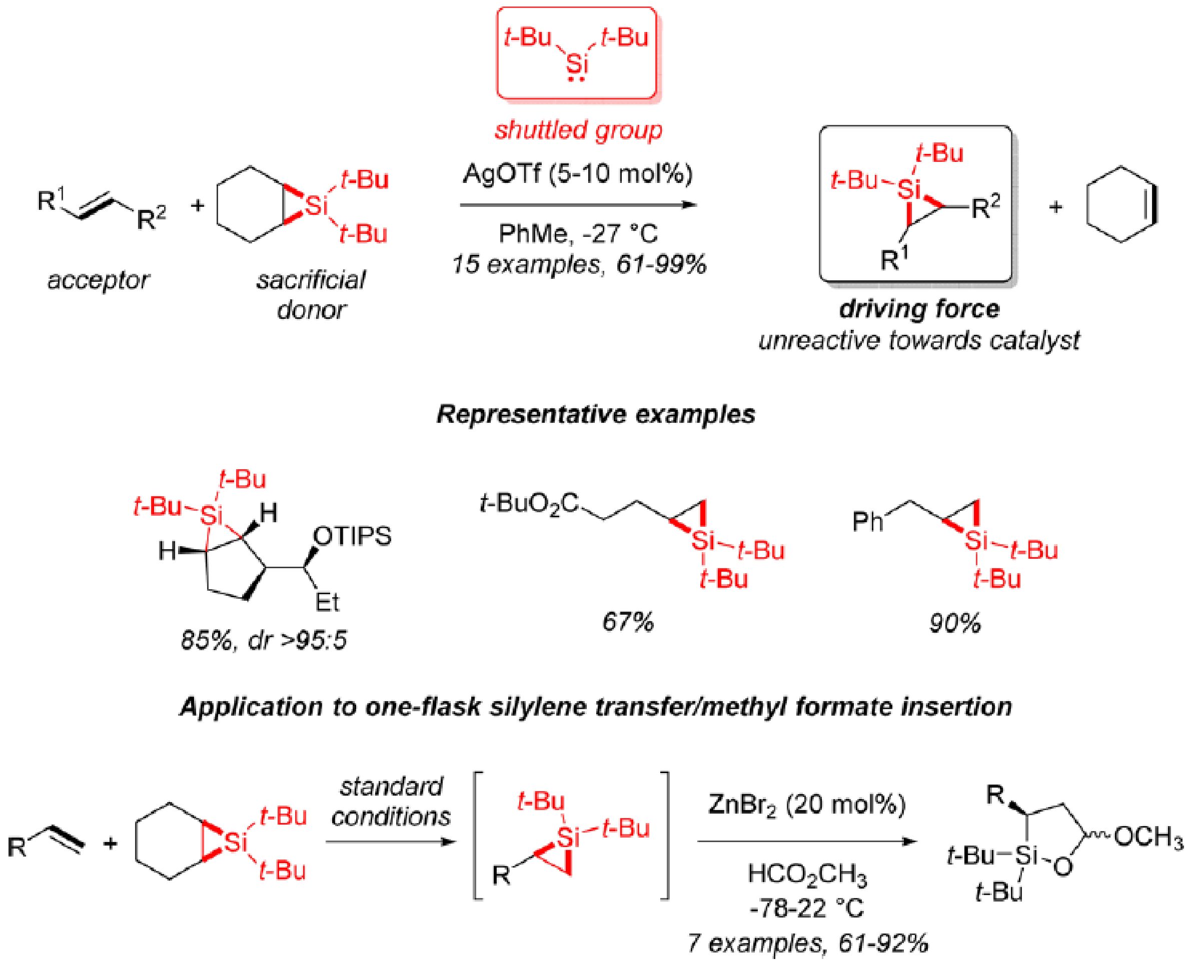


Reaction mechanism

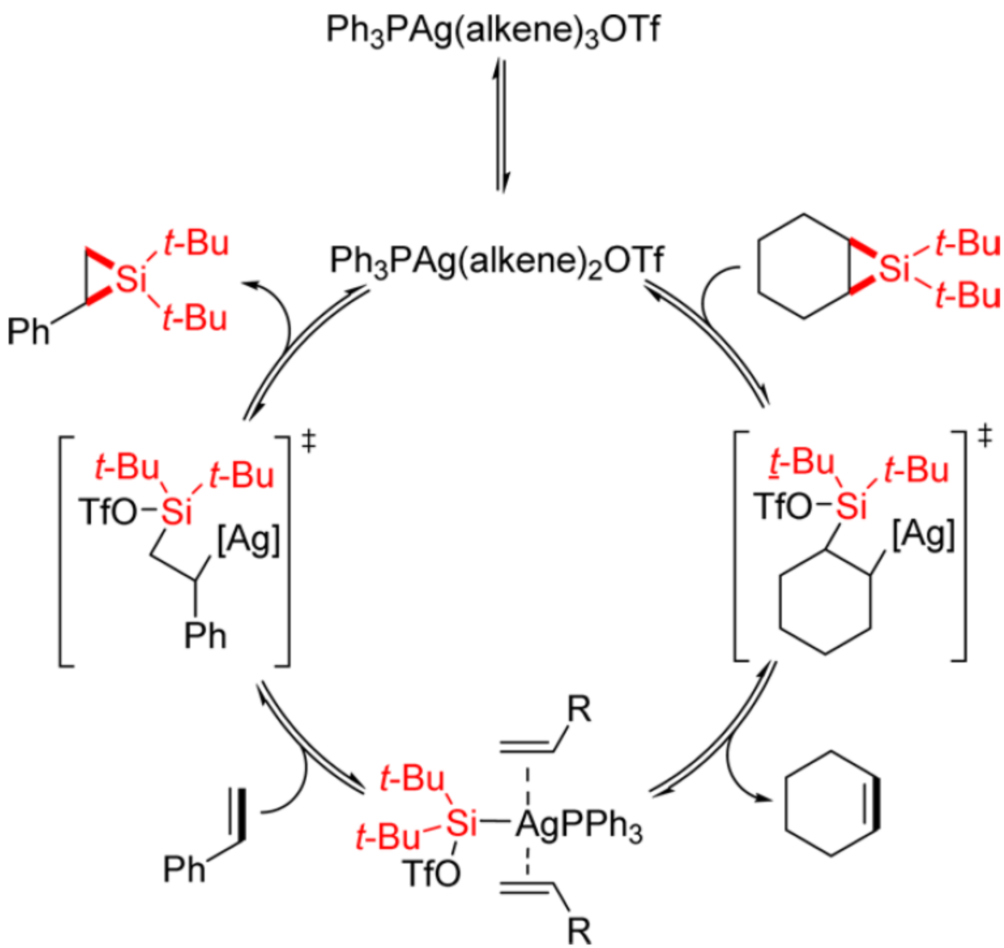


Thomas, S. P., *et at. J. Am. Chem. Soc.* **2012**, *134*, 11900.

5. Catalytic Transfer Silacyclopropanation:



Woerpel, K. A., *et al. J. Am. Chem. Soc.* **2004**, *126*, 9993


Ph3PAg(alkene)3OTf
Ph3PAg(alkene)2OTf
t-Bu
Si
t-Bu
Ph
t-Bu
t-Bu
TfO
Si
[Ag]
Ph
‡
t-Bu
t-Bu
TfO
Si
[Ag]
‡
t-Bu
t-Bu
Si
TfO
AgPPh3
R
R
Ph

Thanks for Your Attention！