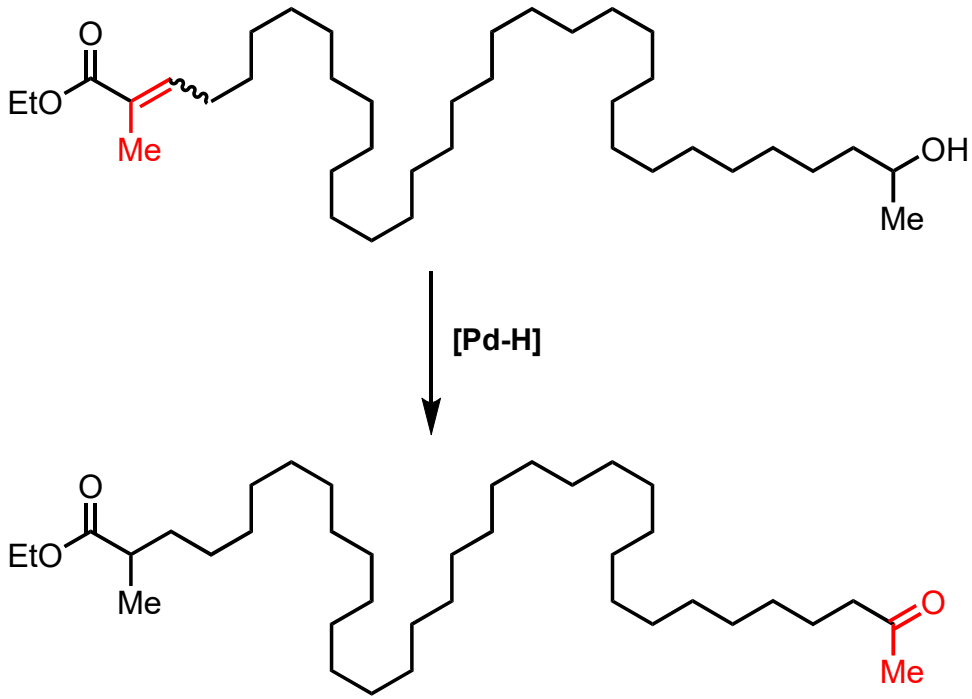
Chain-Walking Processes to Effect Remote Functionalization



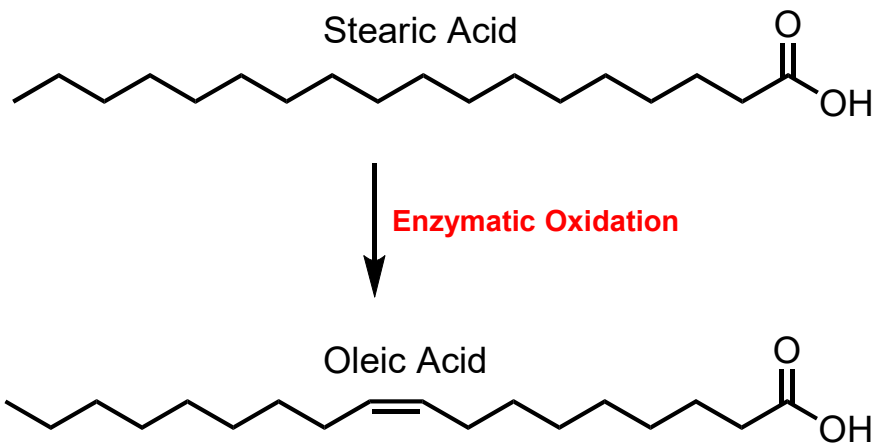
Vincent Kassel

05-29-2018

Presentation Overview

- **Definition of remote functionalization and brief historical perspective.**
- Historical development of metal-mediated chain walking processes and mechanistic paradigms.
- Survey 1,2-hydrogen shift processes from the literature as well as mechanistic investigations.
- Survey 1,3-hydrogen shift processes from the literature.
- Future directions and concluding remarks.

Early Contributions to the Field



"One aspect of biochemistry which was particularly intriguing was the ability of certain enzymes to carry out selective functionalizations of hydrocarbon segments of a molecule remote from any functional groups. An example is the enzymatic conversion of stearic to oleic acid. By contrast, selective chemical reactions normally must be in the vicinity of, and directed by, the already present functional groups of the substrate. Thus we set as a particular target the development of 'remote oxidation' or 'remote functionalization' reactions".

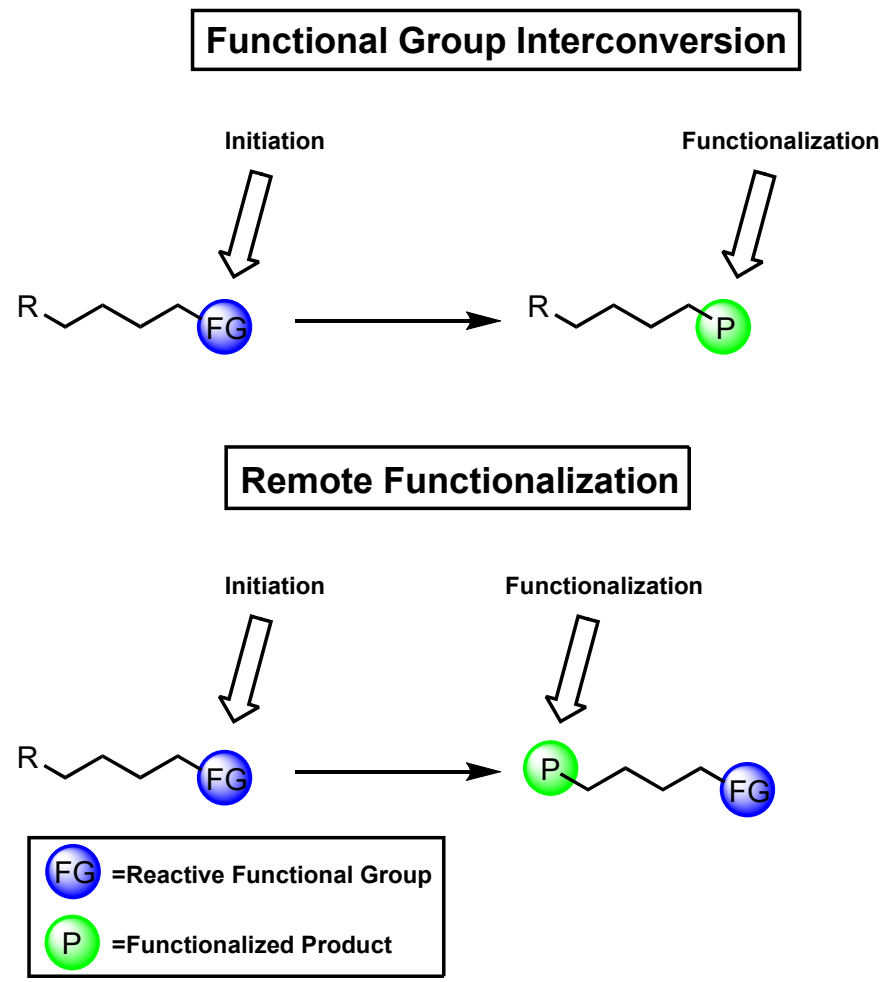
Breslow, R. *Acc. Chem. Res*. **1980**, *13*, 170.

Defining Remote Functionalization

- "An initial interaction of a functional group leading to a selective reaction at a distal position".

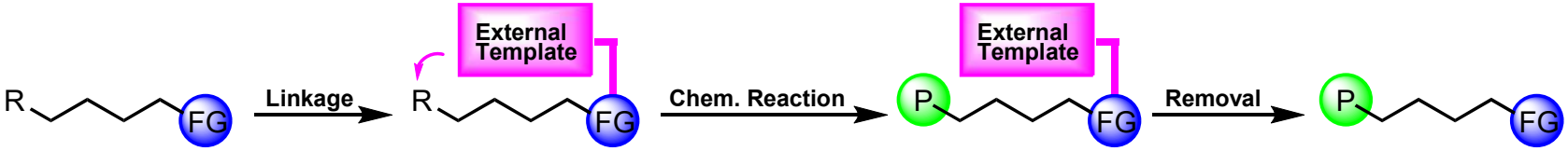
-Marek et al.

- Distance of 2-3 atoms between reactive functional group (FG) and functionalized position (P) is generally considered "remote".



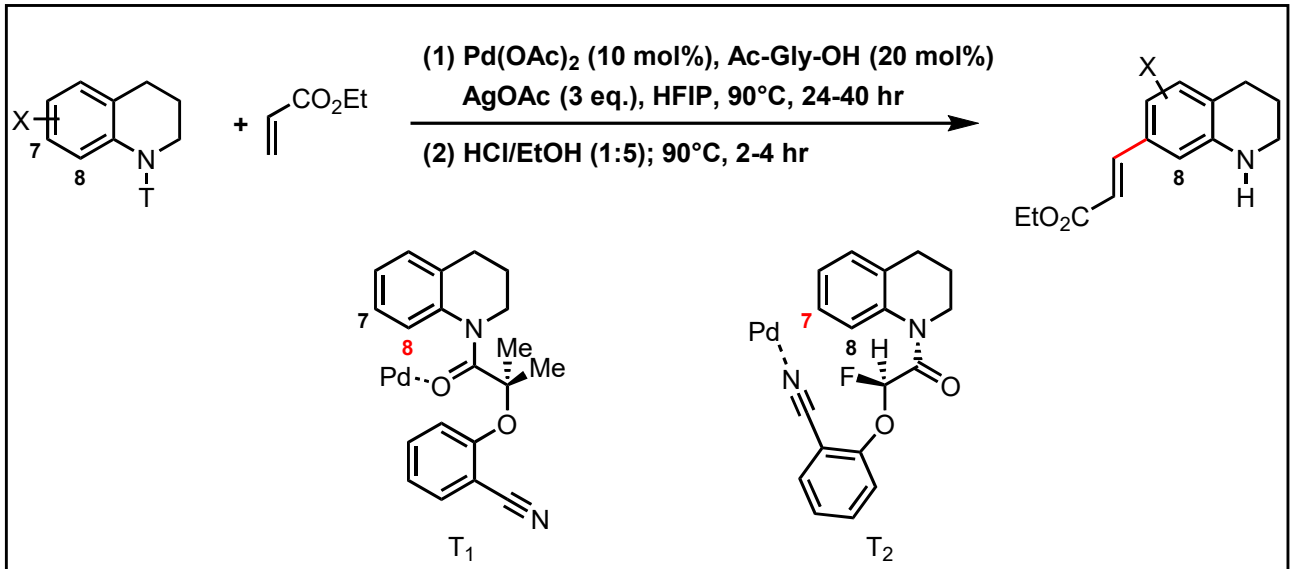
Vasseur, A.; Bruffaerts, J.; Marek, I. *Nat. Chem.* **2016**, *8*, 209.

External Remote Induction



FG =Reactive Functional Group

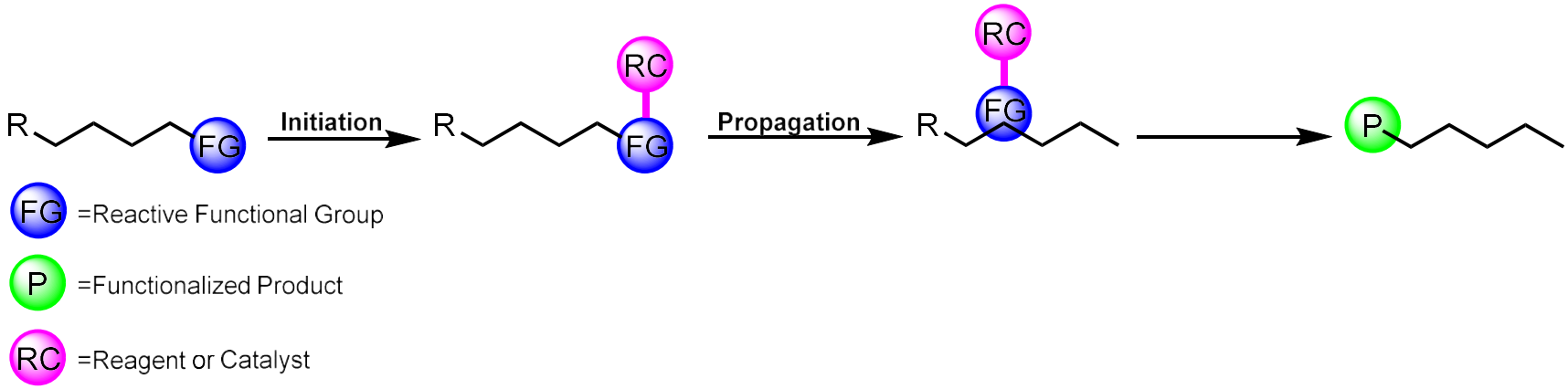
P =Functionalized Product

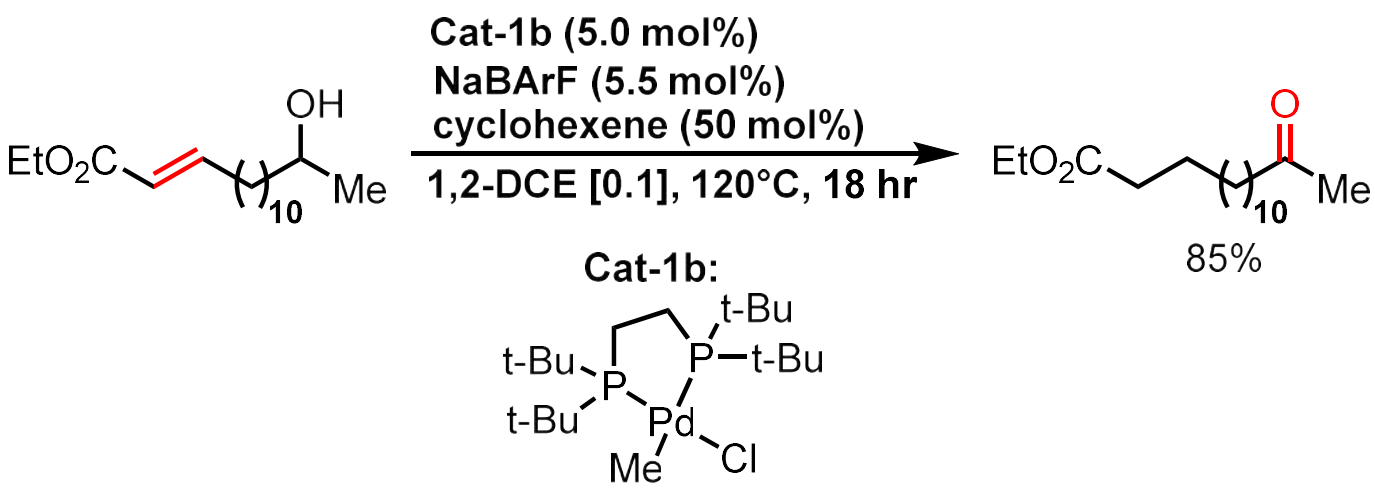


Tang, R. Y.; Li, G.; Yu, J. Q. *Nature* **2014**, *507*, 215.

Vasseur, A.; Bruffaerts, J.; Marek, I. *Nat. Chem.* **2016**, *8*, 209.

Internal Remote Induction





Lin, L.; Romano, C.; Mazet, C. *J. Am. Chem. Soc.* **2016**, *138*, 10344.

Vasseur, A.; Bruffaerts, J.; Marek, I. *Nat. Chem.* **2016**, *8*, 209.

Presentation Overview

- Definition of remote functionalization and brief historical perspective.
- **Historical development of metal-mediated chain walking processes and mechanistic paradigms.**
- Survey 1,2-hydrogen shift processes from the literature.
- Survey 1,3-hydrogen shift processes from the literature.
- Future directions and concluding remarks.

History of Olefin Isomerization

- Transition metal-mediated olefin isomerization known from Fischer-Tropsch hydroformylation processes.

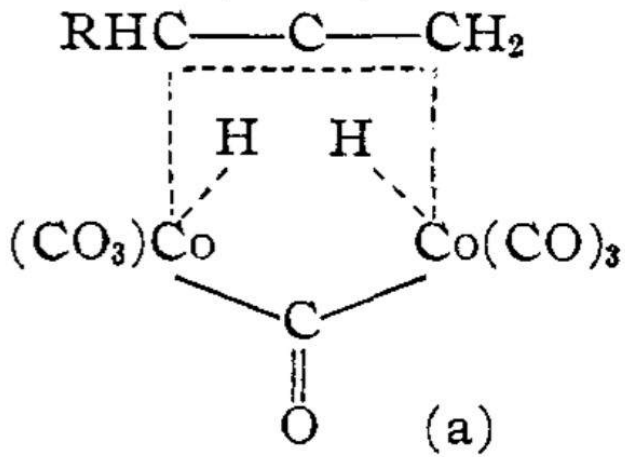
- "We shall consider, first, the double bond isomerization which occurs under hydroformylation conditions. Asinger and Berg found that 1-dodecene was isomerized to a mixture which consisted of all possible double bond isomers in almost equal ratios when the olefin was treated with either a Fischer-Tropsch cobalt catalyst or cobalt metal..."

P. Asinger and O. Berg, *Ber.*, **1955**, *88*, 445.

Wender, I.; Metlin, S.; Ergun, E.; Steinberg, H. W.; Greenfield, H. *J. Am. Chem. Soc.* **1956**, *78*, 5401.

History of Olefin Isomerization

(17) Some mechanism must exist for the facile movement of hydrogen along the carbon chain. R. B. Anderson, of this Laboratory, has suggested that hydrogen atoms are transferred from one part of the molecule to the other by interaction with the cobalt atoms. We may perhaps write the following structure to indicate a manner in which the olefin may be bonded in complex (a). It is interesting that allenes,

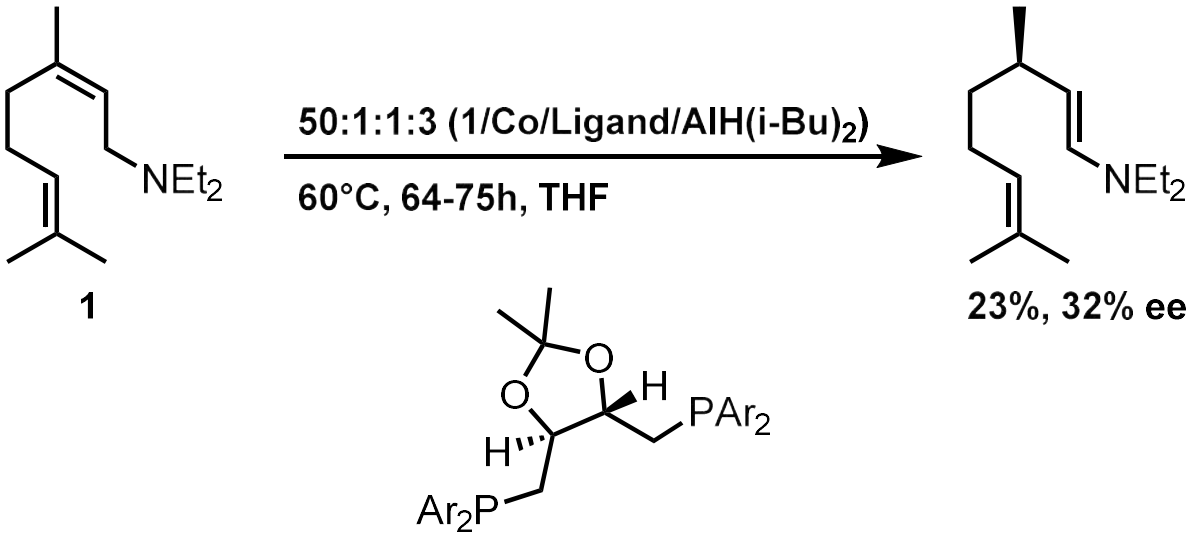


(a)

$RCH{=}C{=}CH_2$ are polymerized by dicobalt octacarbonyl at room temperature (see H. Greenfield, I. Wender and J. Wotiz, *J. Org. Chem.*, **21**, 875 (1956).

Wender, I.; Metlin, S.; Ergun, E.; Steinberg, H. W.; Greenfield, H. *J. Am. Chem. Soc.* **1956**, *78*, 5401.

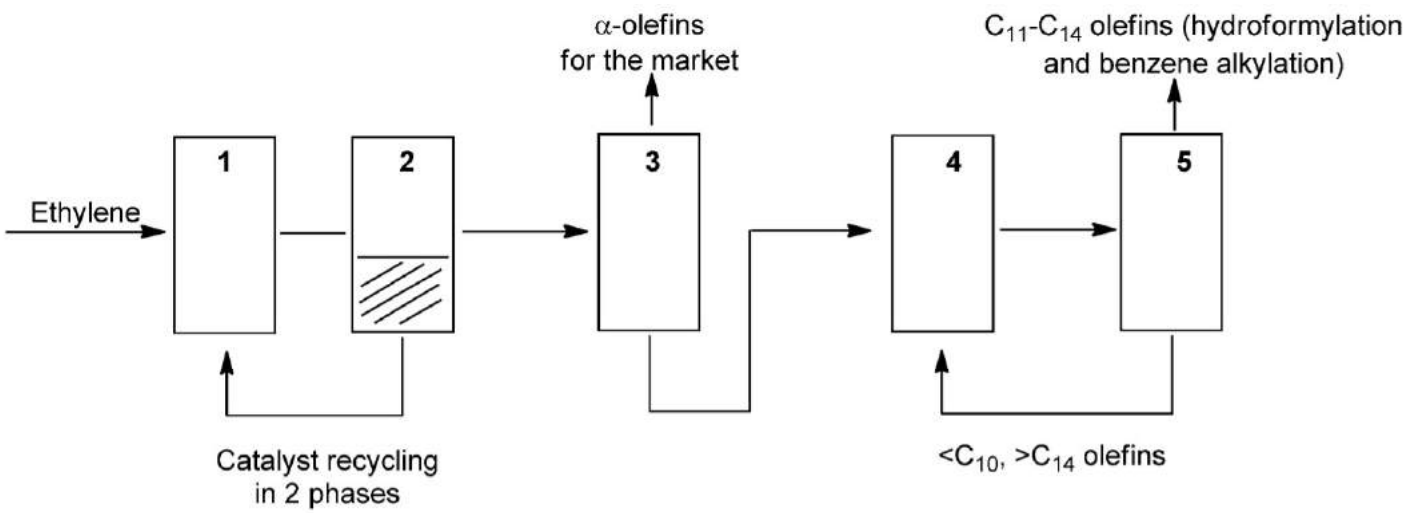
Notable Early Synthetic Examples



Kumobayashi, H.; Akutagawa, S.; Otsuka, S. *J. Am. Chem. Soc.* **1978**, *100*, 3949.

Notable Early Synthetic Examples

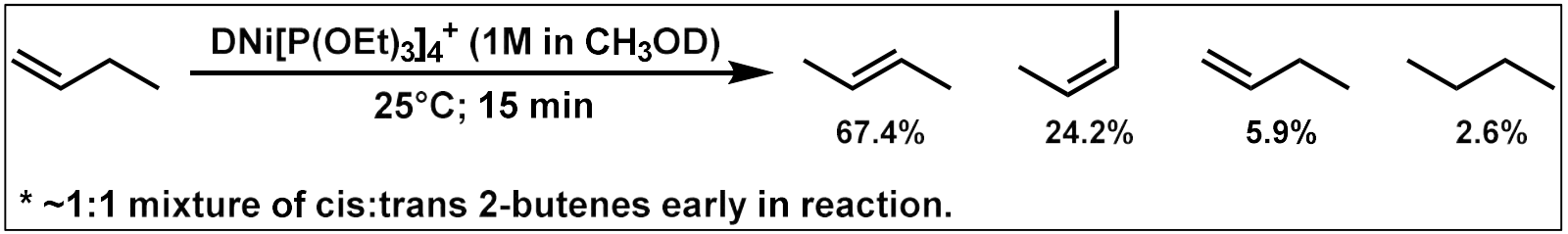
Shell Higher Olefin Process (SHOP)



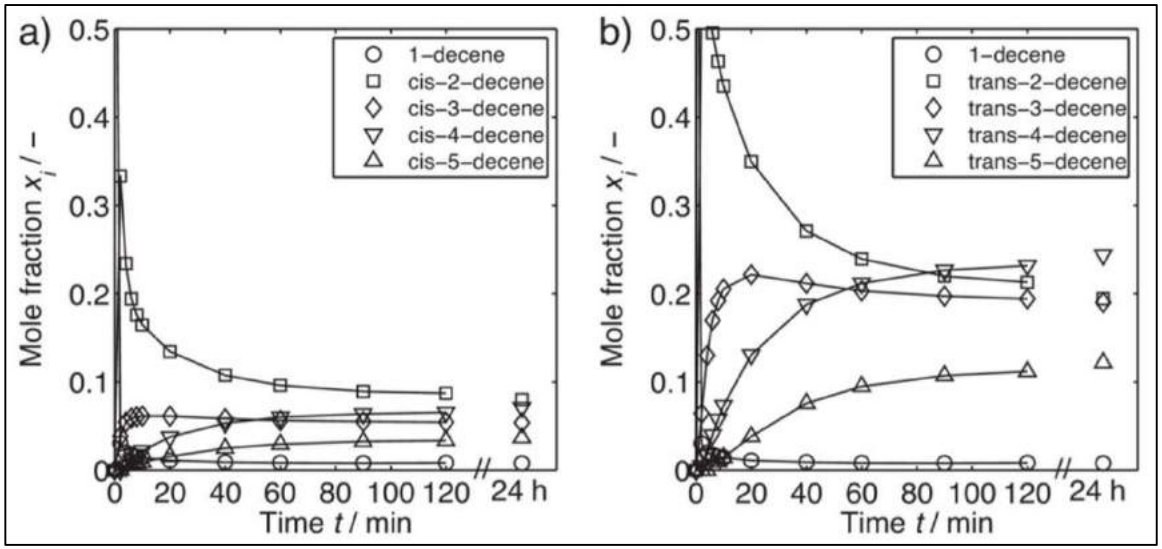
1 Oligomerization
2 Catalyst recycling
3 Destillation
4 Isomerization
5 Metathesis

Keim, W. *Angew. Chem., Int. Ed.* **2013**, *52*, 12492.

Equilibrium Trends



Tolman, C. A. *J. Am. Chem. Soc*. **1972**, *94*, 2994.

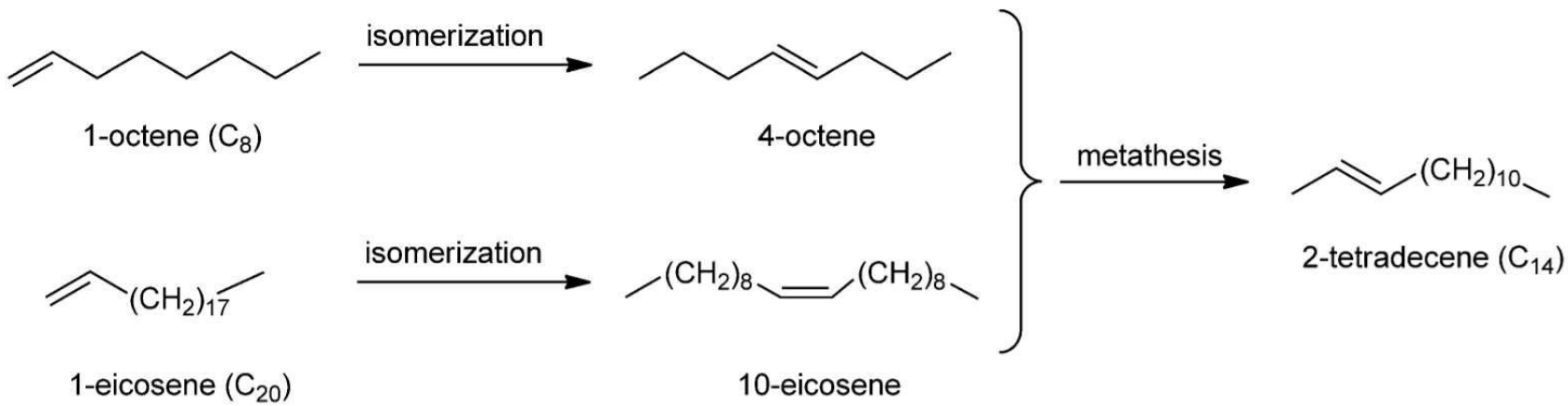


A. Jörke, E. Kohls, S. Triemer, A. Seidel-Morgenstern, C. Hamel, M. Stein, *Chem. Eng. Process. Process Intensif*. **2016**, *102*, 229.

Experimentally time-resolved observed composition of all n-decene isomers (378 K, 3 bar N_2). Molar fraction relative to the initial amount of substance of 1-decene; (a) 1-decene and cis isomers; (b) 1-decene and trans isomers. Catalyst: Rh(BIPHEPHOS).

Notable Early Synthetic Examples

Shell Higher Olefin Process (SHOP)

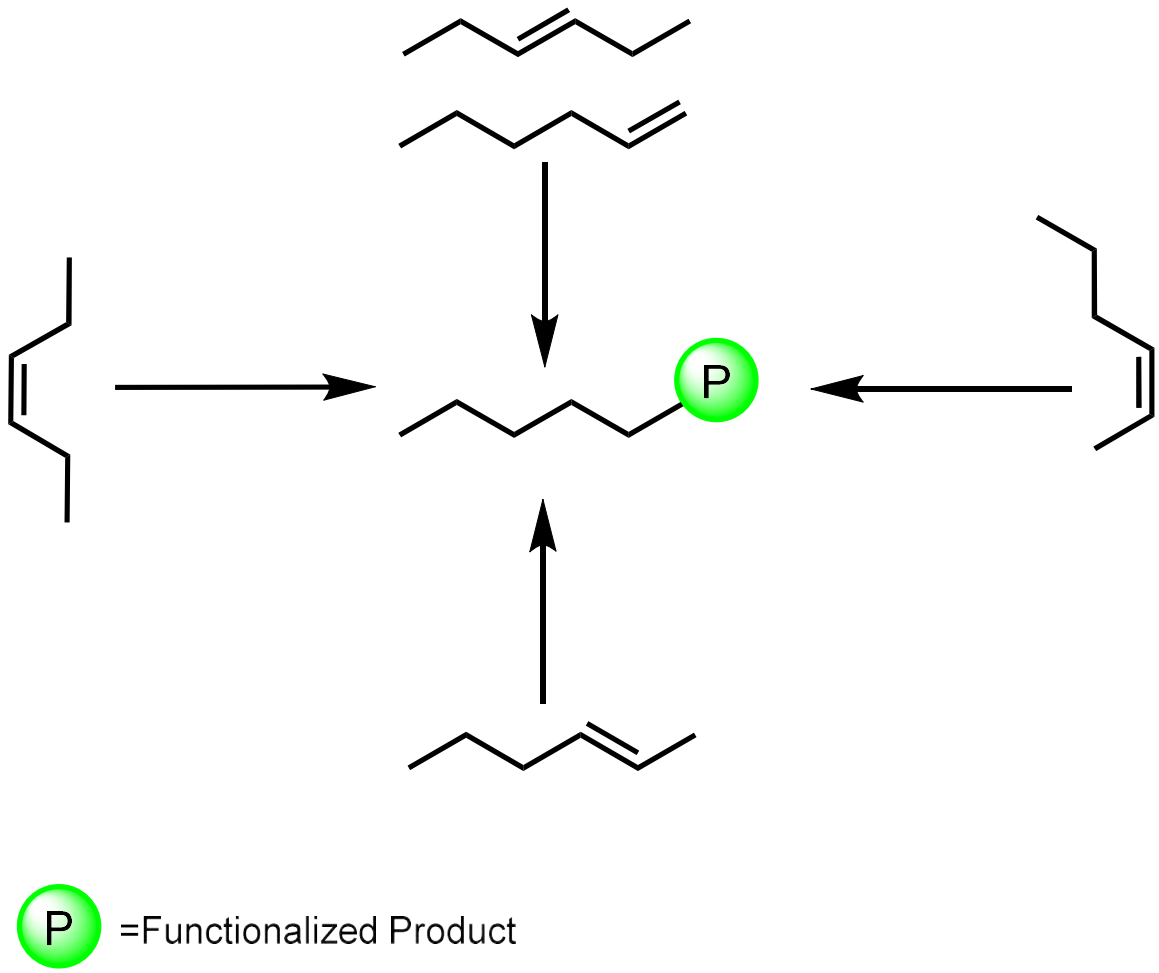


Metathesis of 1-octene and 1-eicosene.

Keim, W. *Angew. Chem., Int. Ed.* **2013**, *52*, 12492.

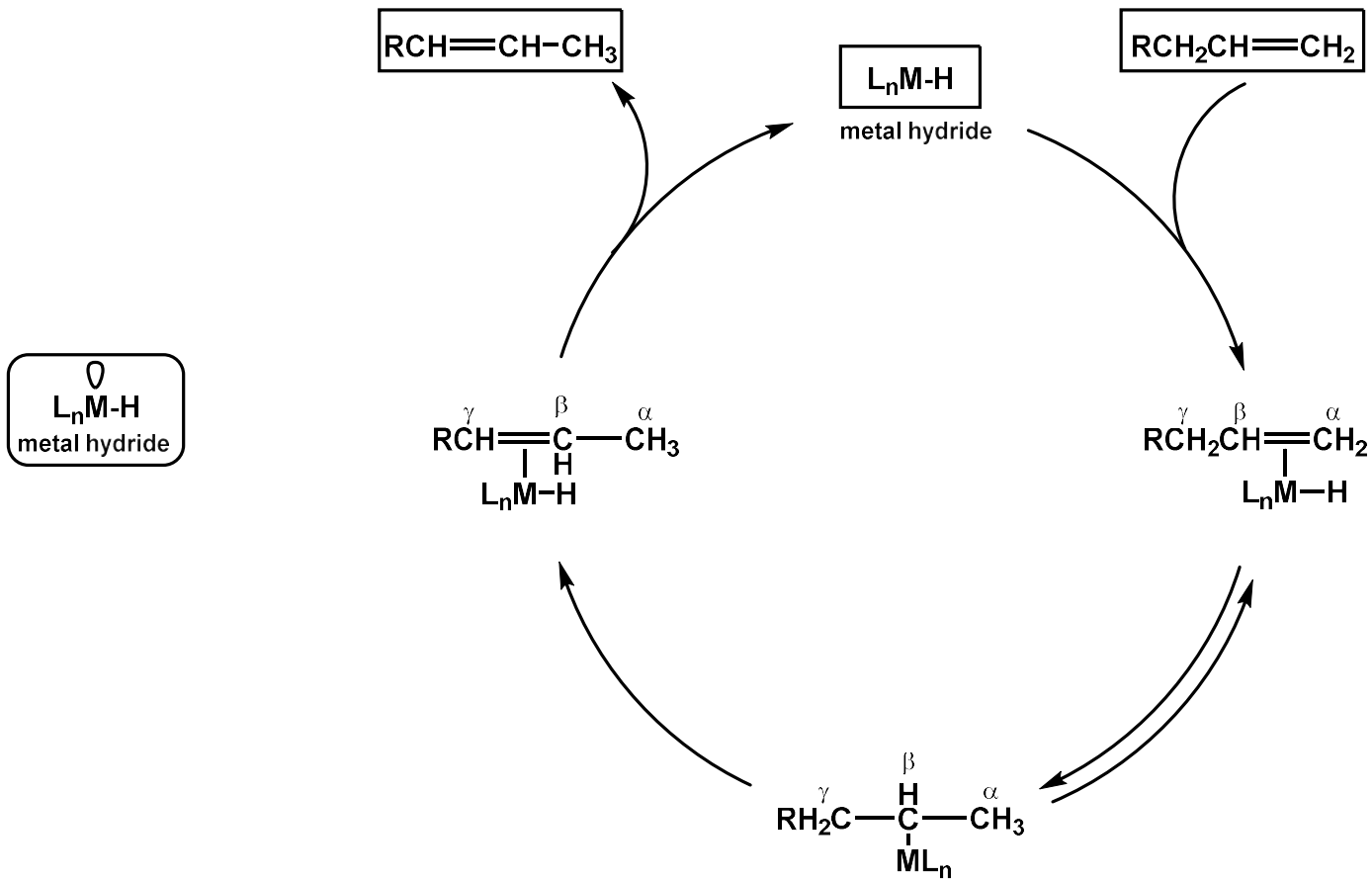
Synthetic Appeal of Olefin Isomerization

- Alkenes are an abundant and cheap feedstock chemicals.
  Possibility of convergent functionalization funneling olefinic mixtures into a single product.
- With bond migration, substrates undergo refunctionalization in overall redox-neutral manner with no additional chemical waste.



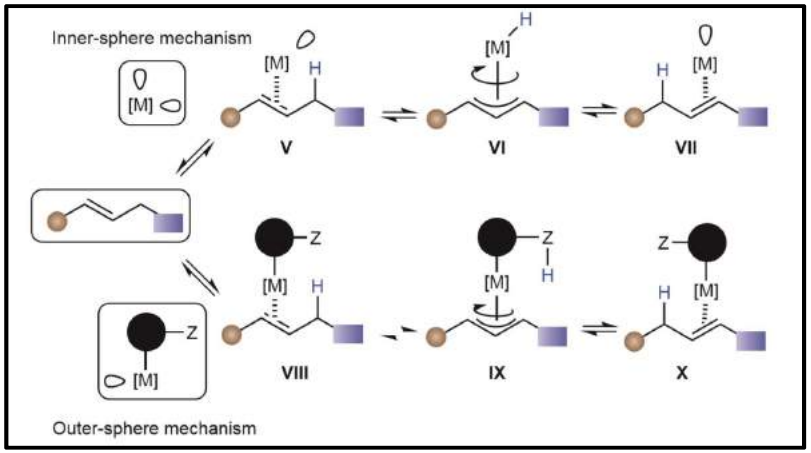
Larionov, E.; Lin, L.; Guénée, L.; Mazet, C. *J. Am. Chem. Soc.* **2014,** *136*, 16882.

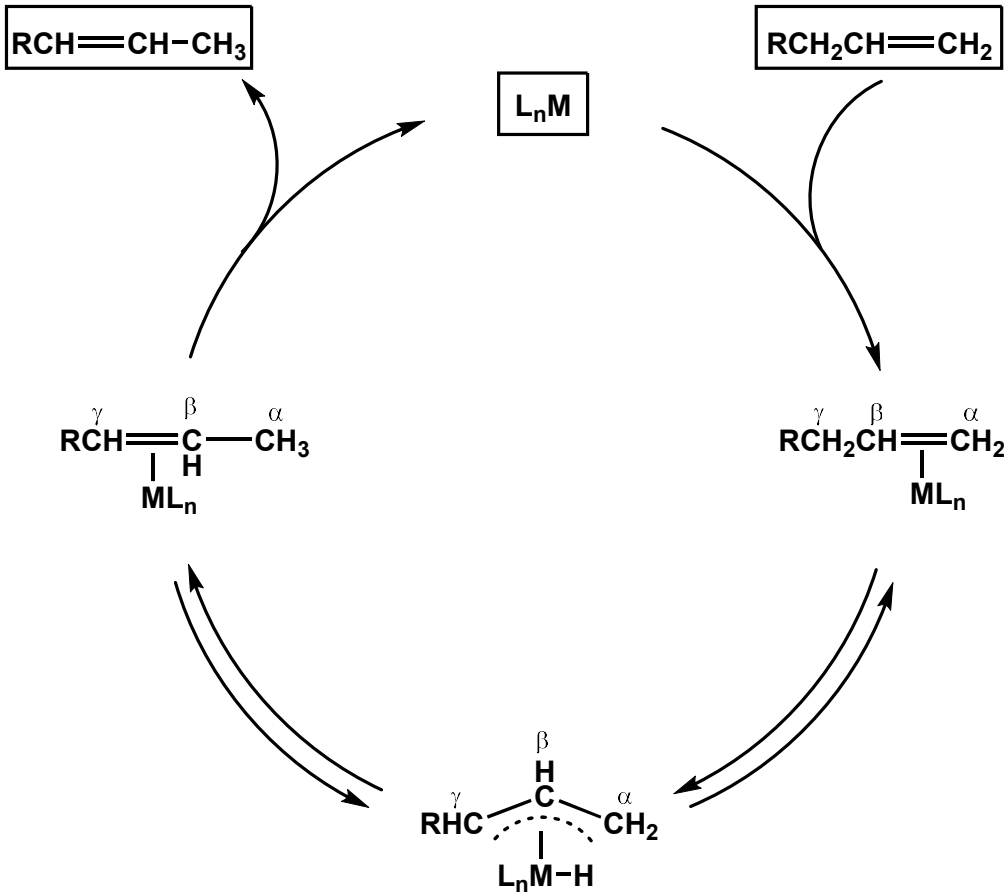
1,2-hydrogen (alkyl) shift



Vasseur, A.; Bruffaerts, J.; Marek, I. *Nat. Chem*. **2016**, *8*, 209.
Applied Homogeneous Catalysis with Organometallic Compounds 2nd edn, 1119–1124

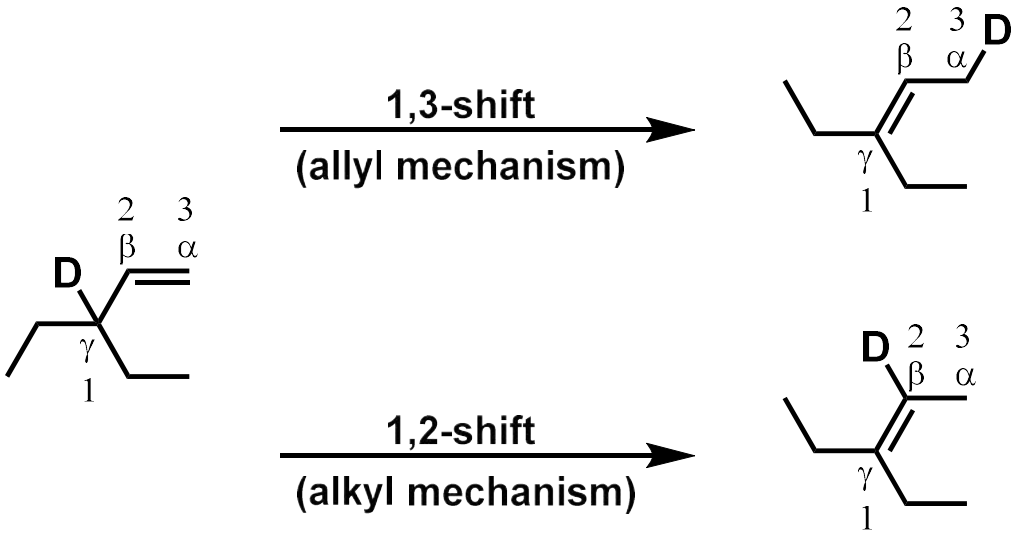
1,3-hydrogen (allyl) shift





Vasseur, A.; Bruffaerts, J.; Marek, I. *Nat. Chem*. **2016**, *8*, 209.
Applied Homogeneous Catalysis with Organometallic Compounds 2nd edn, 1119.

1,2-vs 1,3-Hydrogen Shifts



Applied Homogeneous Catalysis with Organometallic Compounds 2nd edn, 1119.

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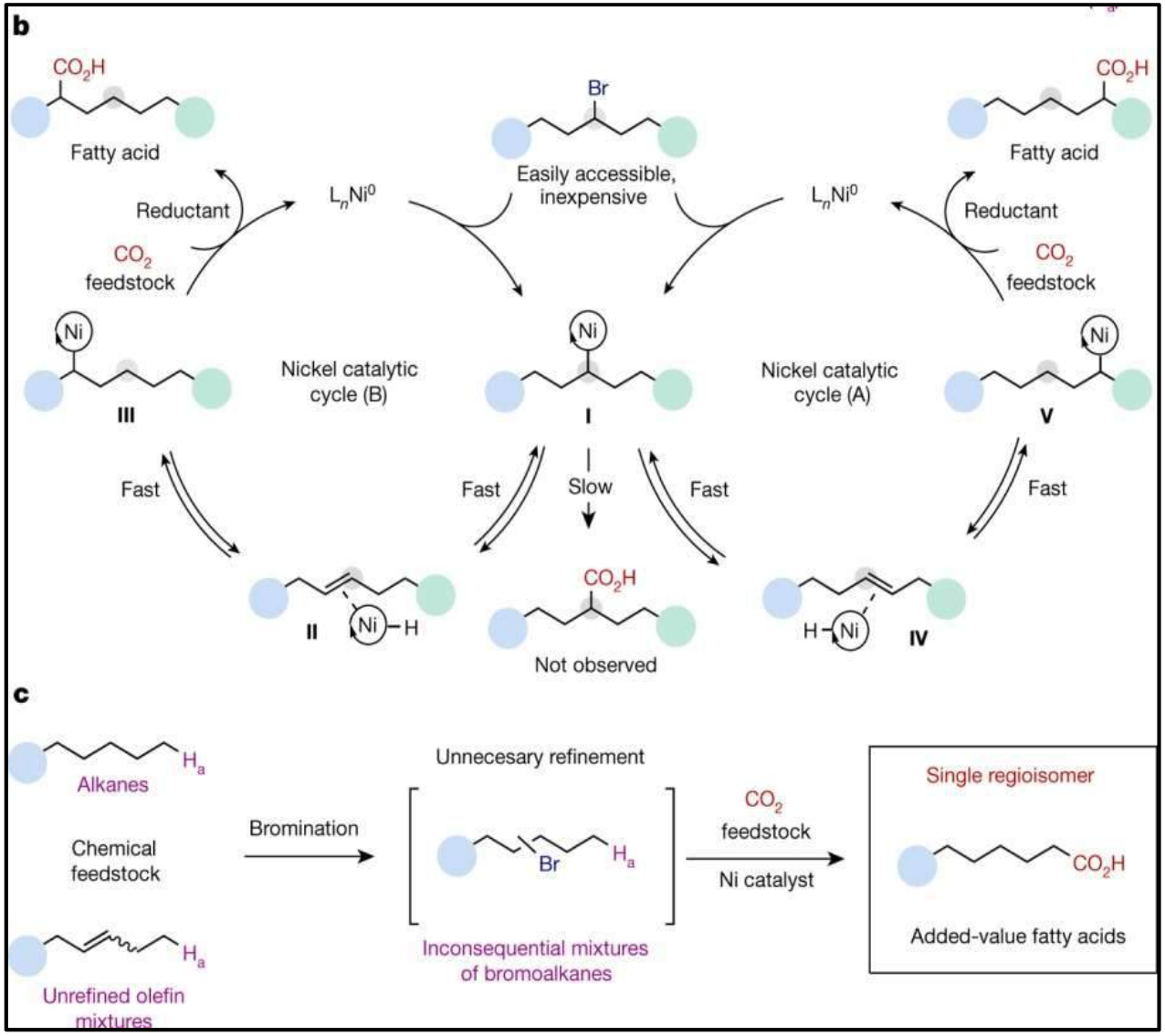
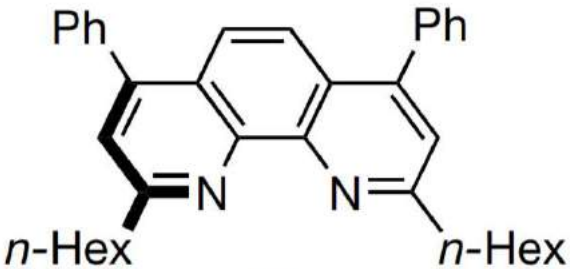
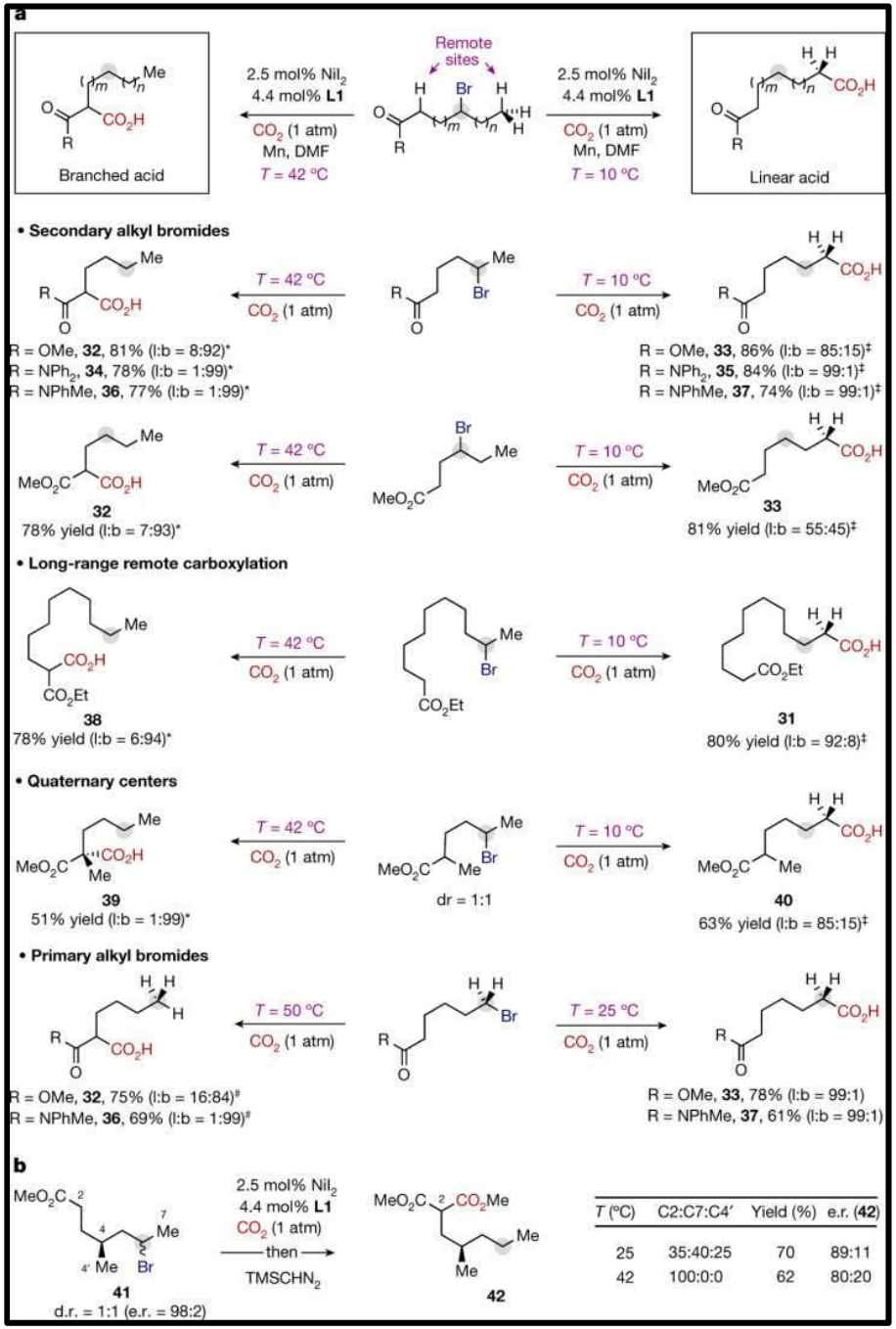
Nickel-Mediated Remote Carboxylation



Juliá-Hernández, F.; Moragas, T.; Cornella, J.; Martin, R. *Nature* **2017**, *545*, 84.



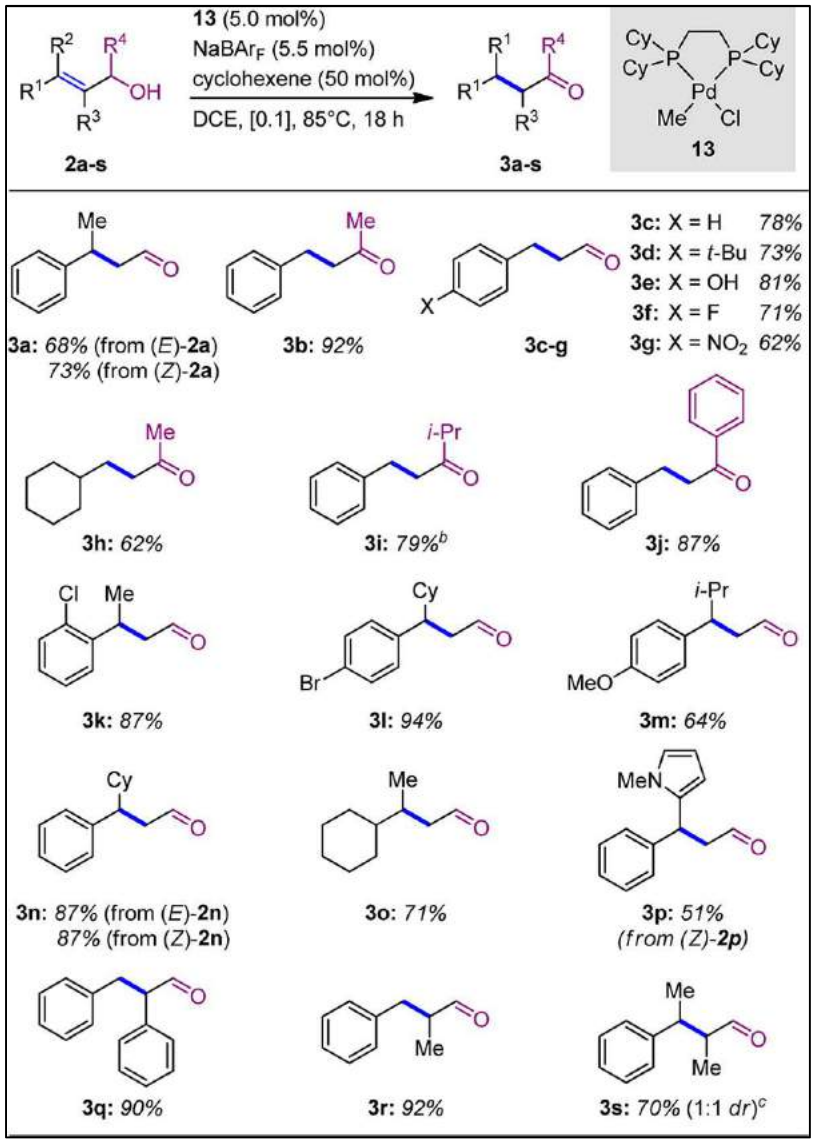
L1

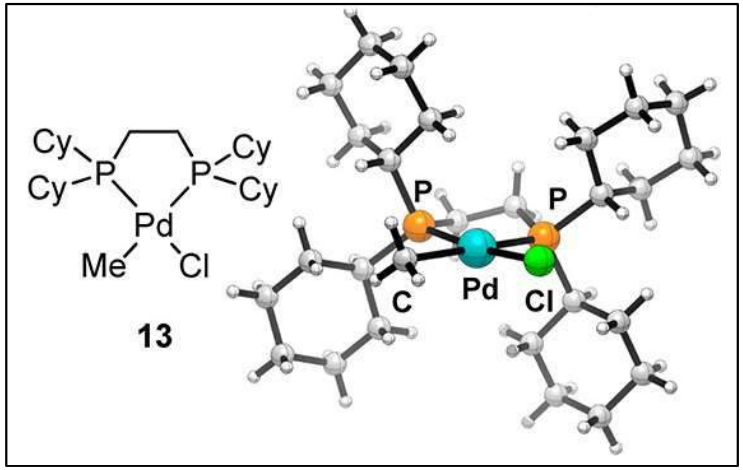


T (°C)	C2:C7:C4′	Yield (%)	e.r. (42)
25	35:40:25	70	89:11
42	100:0:0	62	80:20

Juliá-Hernández, F.; Moragas, T.; Cornella, J.; Martin, R. *Nature* **2017**, *545*, 84.

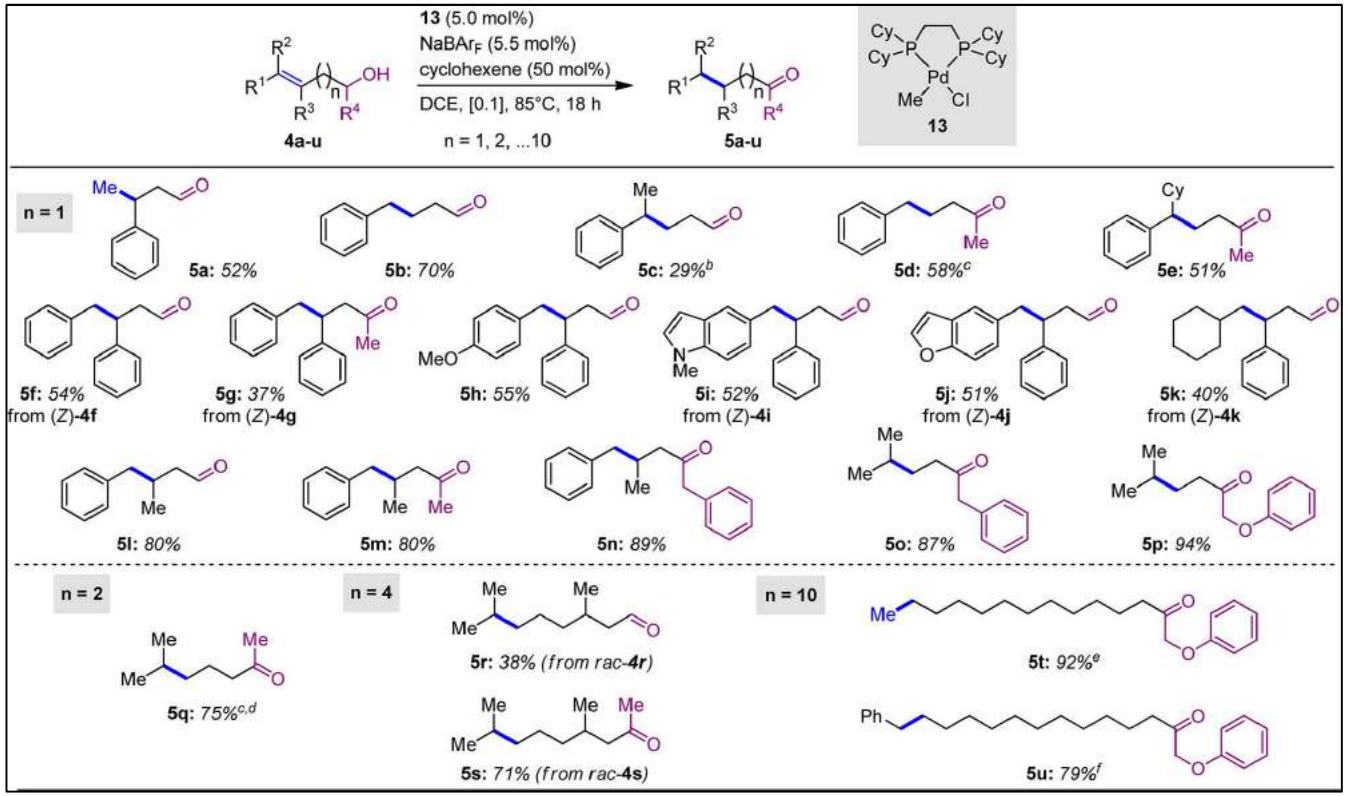
Isomerization of Allylic Alcohols

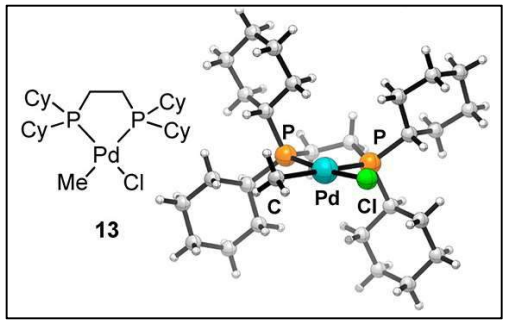




Larionov, E.; Lin, L.; Guénée, L.; Mazet, C. *J. Am. Chem. Soc.* **2014**, *136*, 16882.

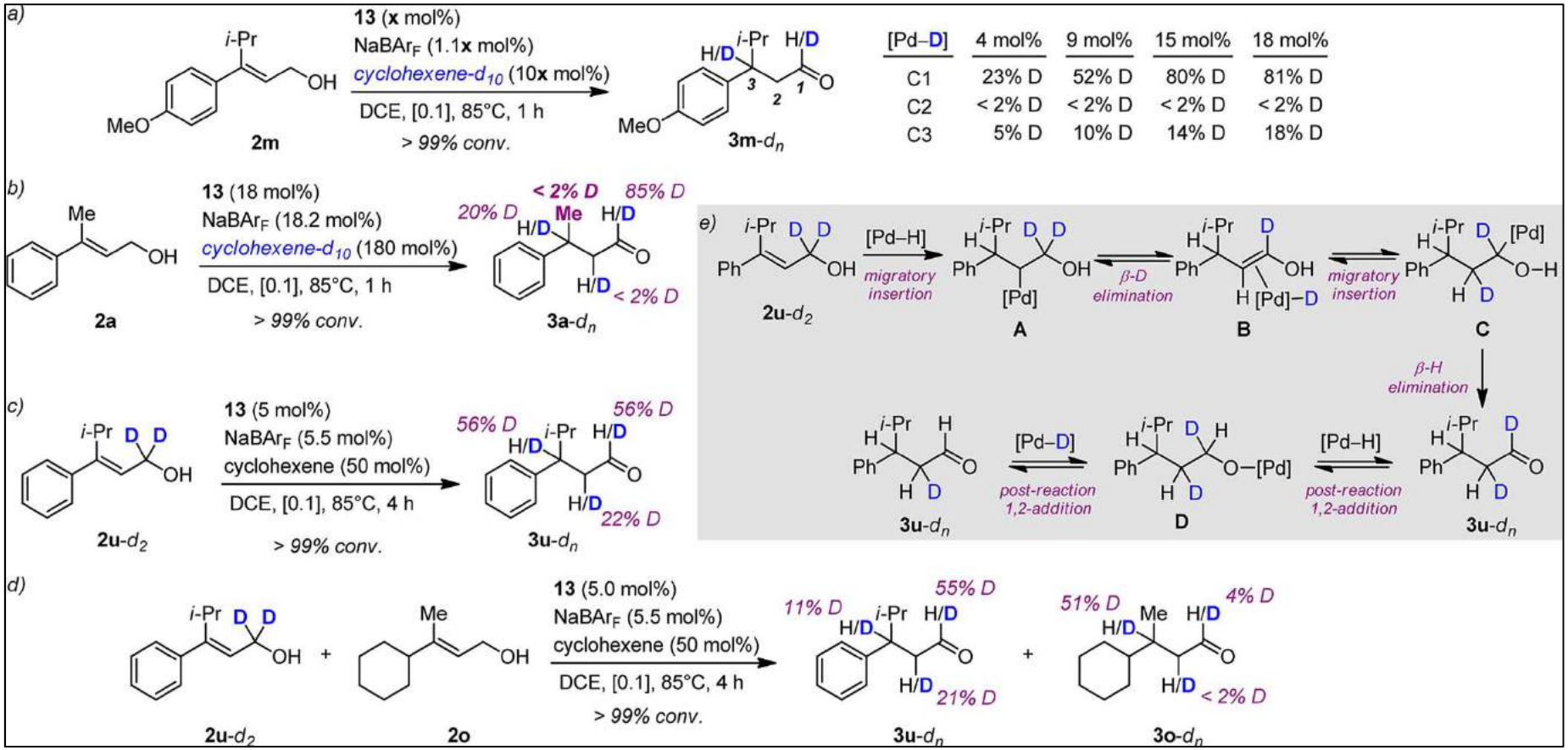
Isomerization of Homoallylic/ Alkenyl Alcohols





Larionov, E.; Lin, L.; Guénée, L.; Mazet, C. *J. Am. Chem. Soc.* **2014**, *136*, 16882.

Deuterium Labeling Experiments

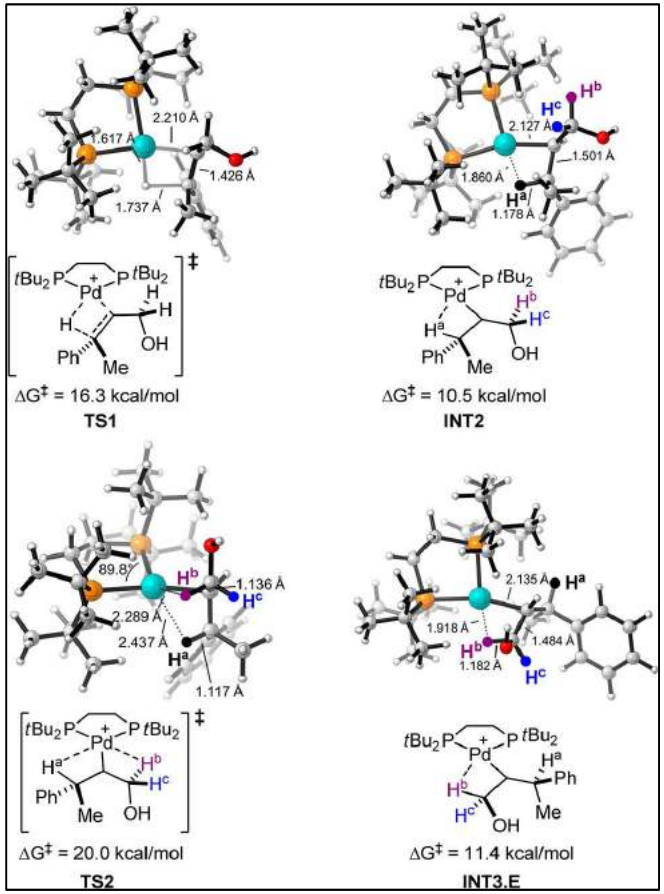


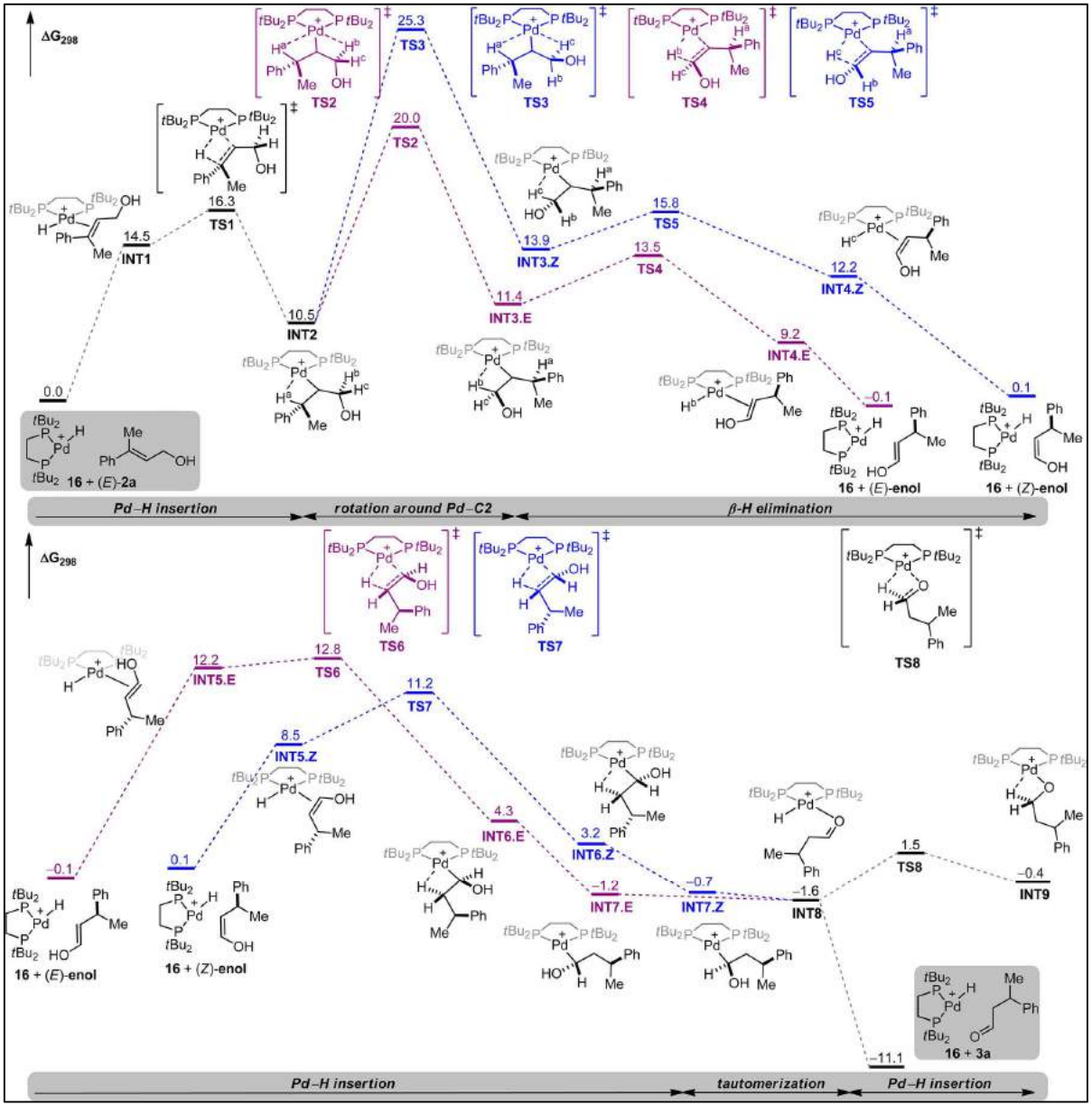
[Pd–D]	4 mol%	9 mol%	15 mol%	18 mol%
C1	23% D	52% D	80% D	81% D
C2	< 2% D	< 2% D	< 2% D	< 2% D
C3	5% D	10% D	14% D	18% D

(a–c) Labeling experiments: (a) with 2m and in situ generation of [Pd–D] using various Pd loadings; (b) with 2a and in situ generation of [Pd–D]; (c) with 2u-*d*2 and in situ generation of [Pd–H]. (d) Crossover experiment. (e) Mechanistic rationale.

Larionov, E.; Lin, L.; Guénée, L.; Mazet, C. *J. Am. Chem. Soc*. **2014**, *136*, 16882.

Computational Investigation of (E)-2a Isomer

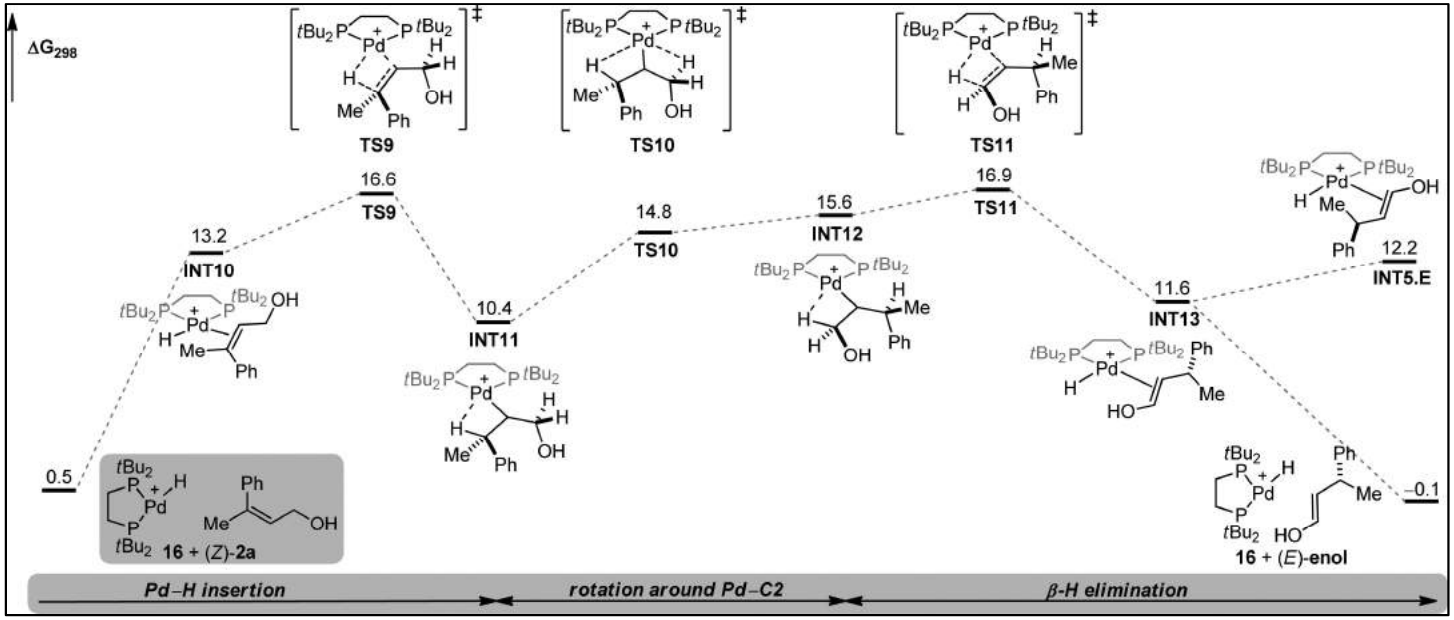


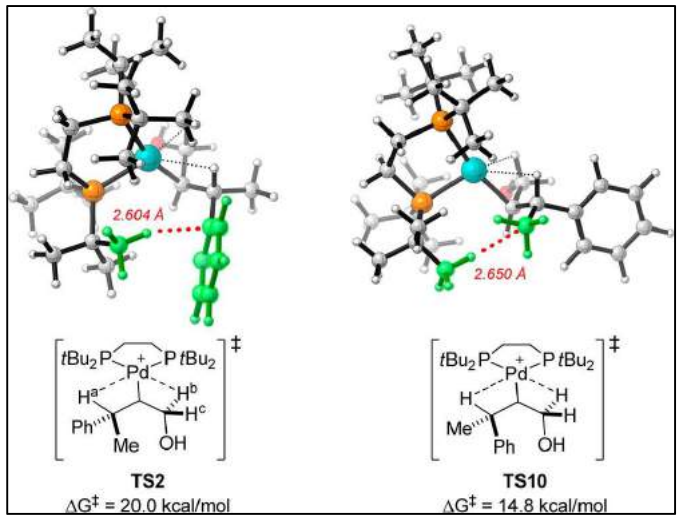


Computed reaction profile for the productive isomerization of (*E*)-2a to 3a. The most relevant intermediates and transition states are represented. DFT method: PCMDCE-B3LYP/[6-311+G(d,p); LANL2DZ]//M06L/[6-31G(d) on C, H, O, P; LANL2DZ on Pd]. Δ*G* values are given in kcal/mol.(25, 26)

Larionov, E.; Lin, L.; Guénée, L.; Mazet, C. *J. Am. Chem. Soc.* **2014**, *136*, 16882.

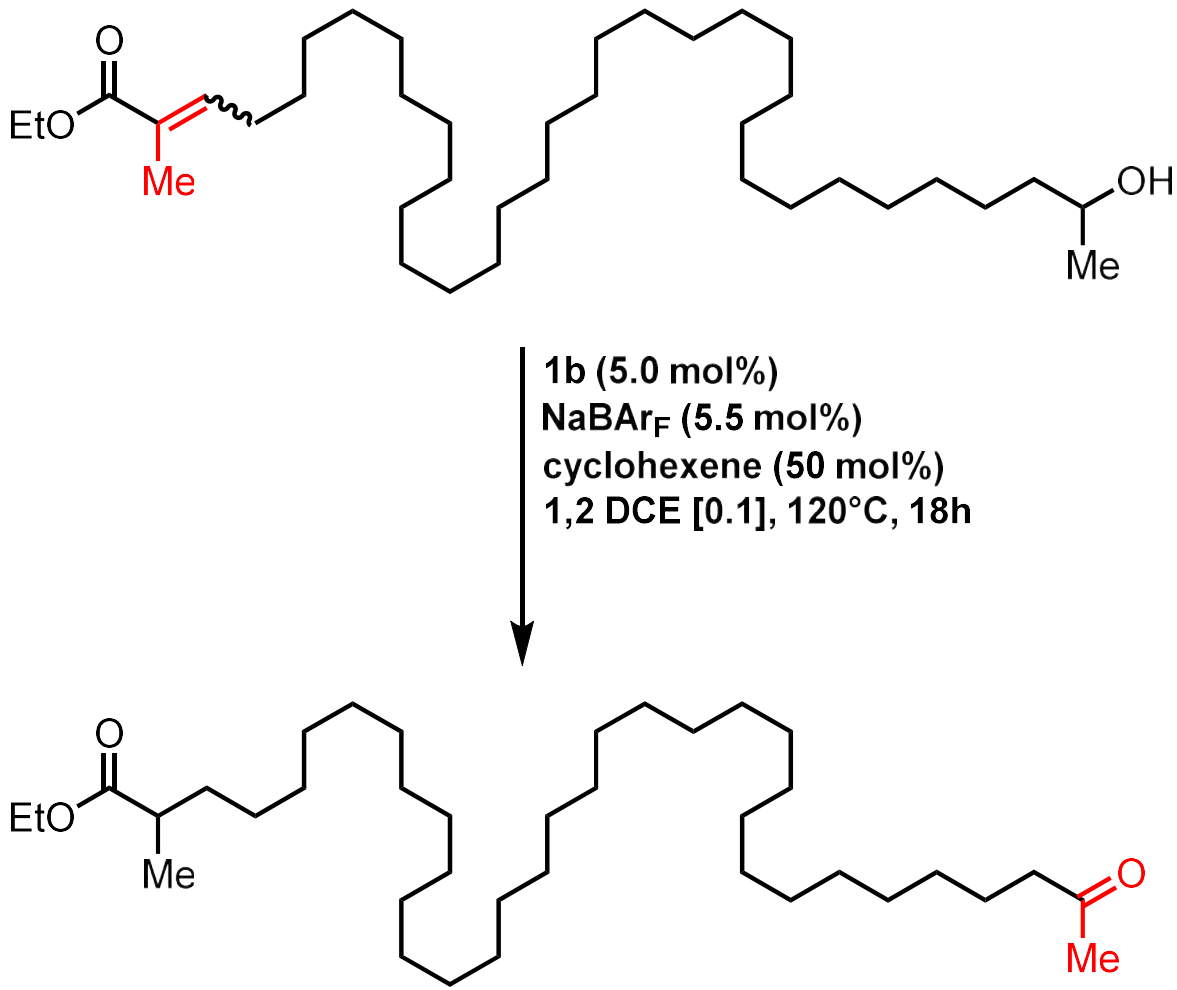
Computational Investigation of (Z)-2a Isomer

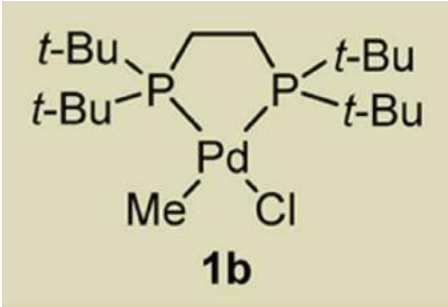




Larionov, E.; Lin, L.; Guénée, L.; Mazet, C. *J. Am. Chem. Soc.* **2014**, *136*, 16882.

1,2-Long Range Champion



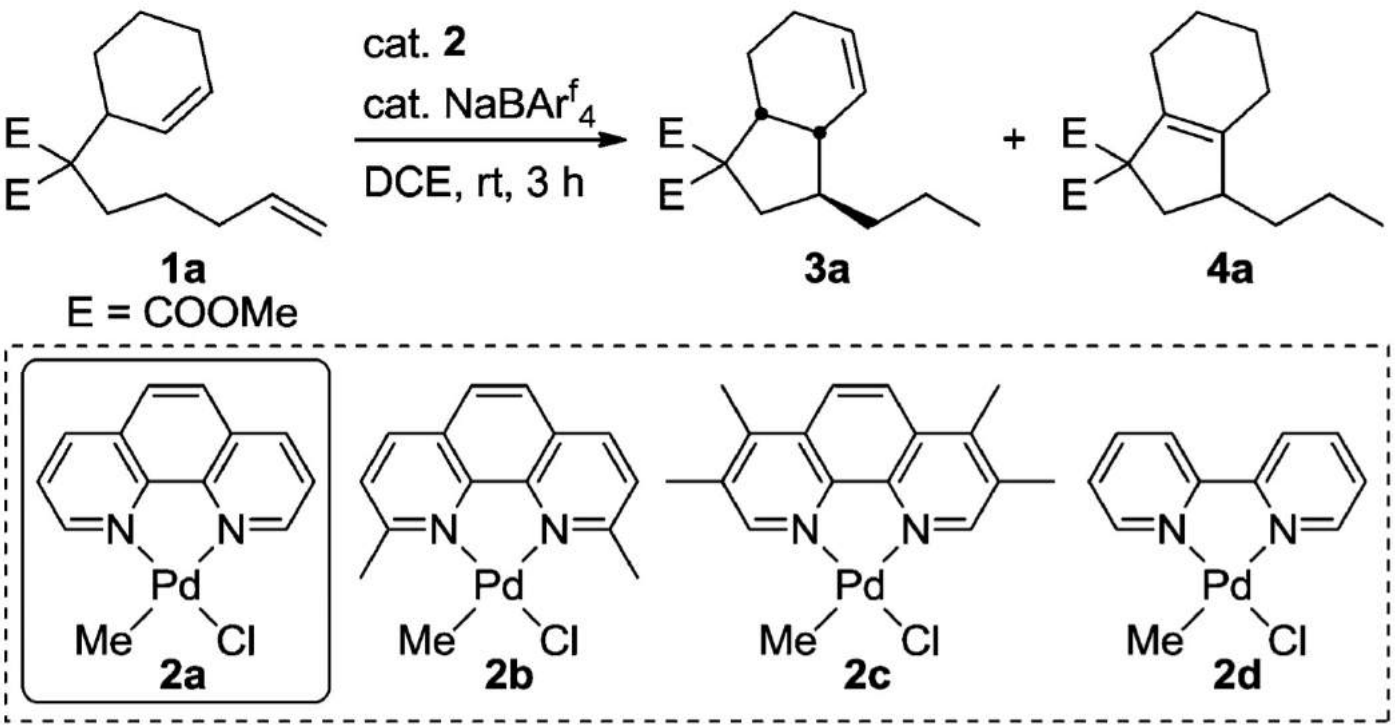


72% Yield

Lin, L.; Romano, C.; Mazet, C. *J. Am. Chem. Soc.* **2016**, *138*, 10344.

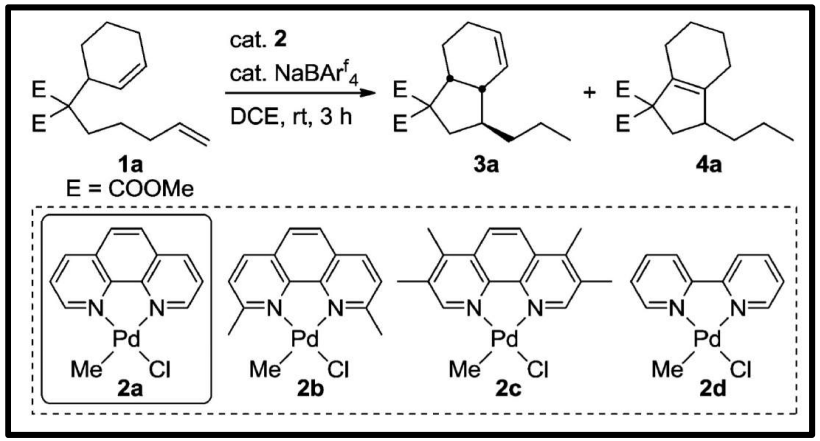
Cycloisomerizations (Group Problem)

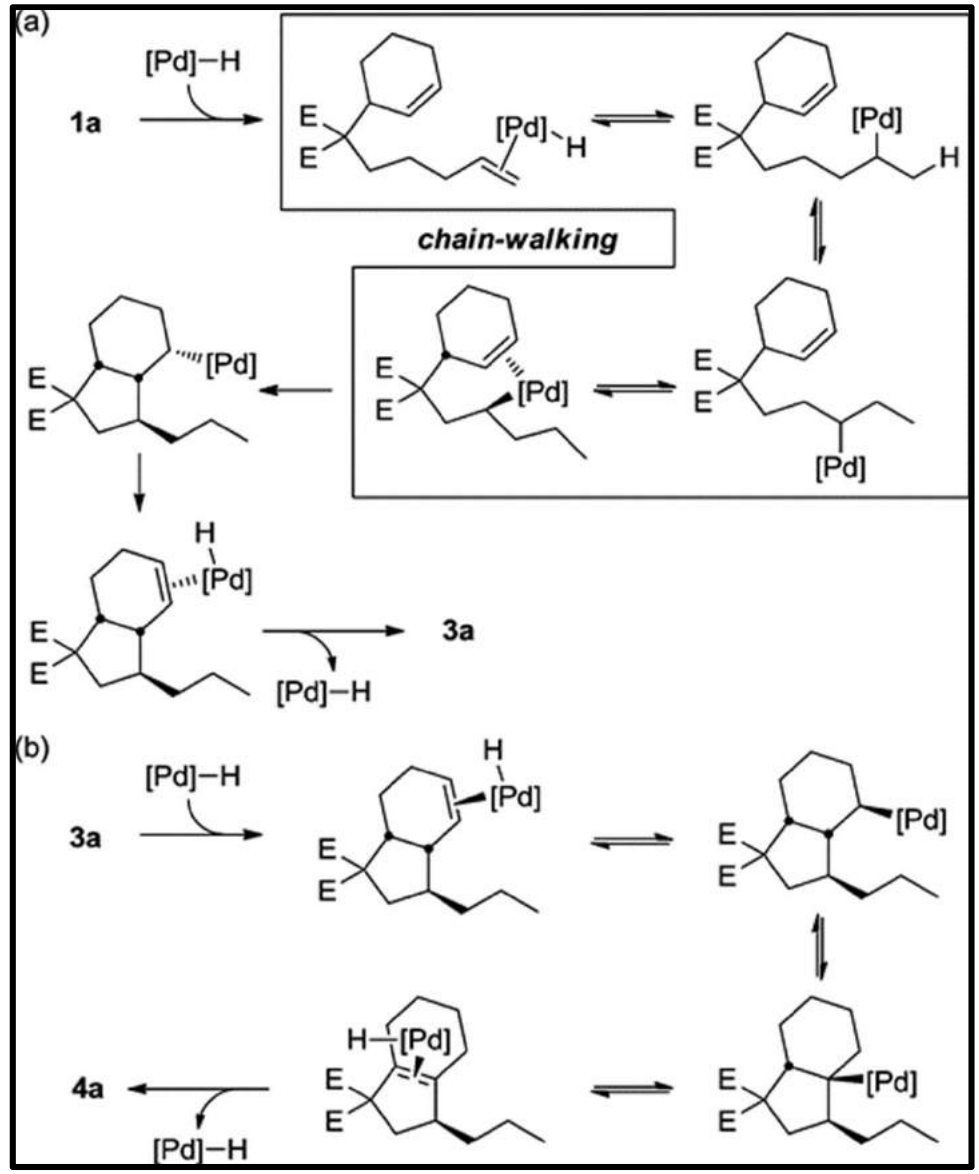
Propose a mechanism that accounts for products 3a and 4a.



Kochi, T.; Hamasaki, T.; Aoyama, Y.; Kawasaki, J.; Kakiuchi, F. *J. Am. Chem. Soc.* **2012**, *134*, 16544.

Group Problem Answer

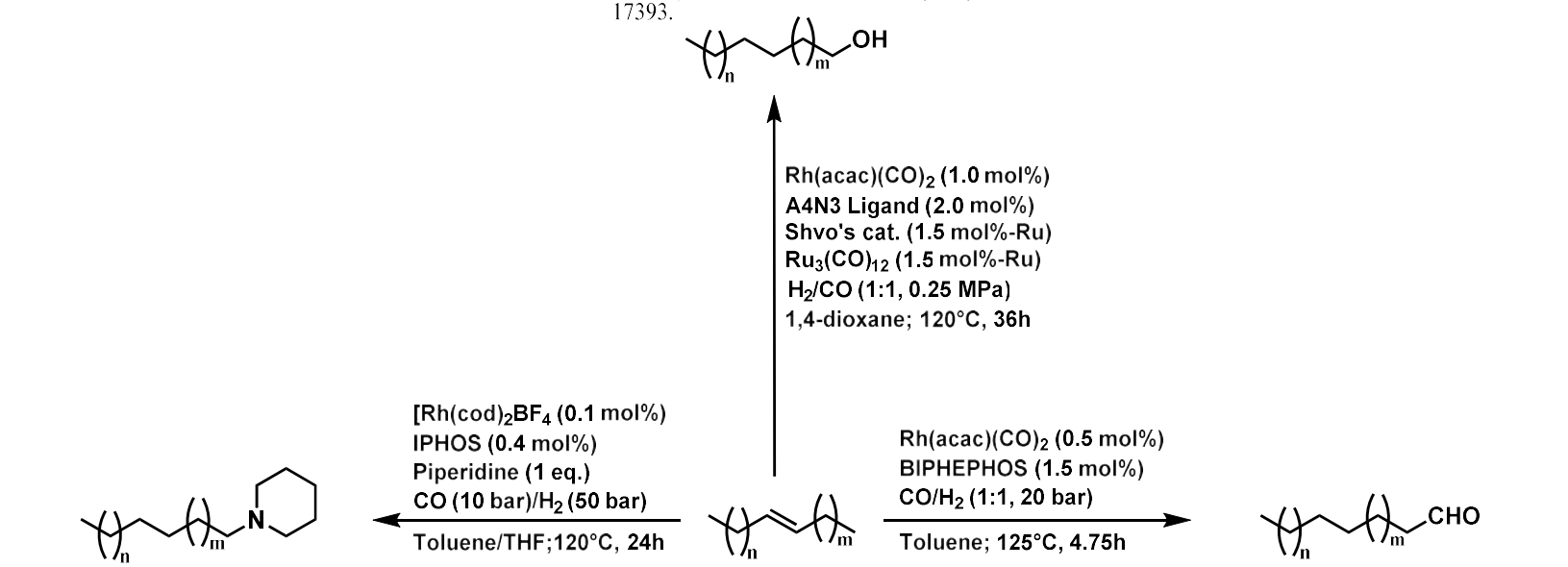




Kochi, T.; Hamasaki, T.; Aoyama, Y.; Kawasaki, J.; Kakiuchi, F. *J. Am. Chem. Soc.* **2012**, *134*, 16544.

Hydroformylation Methods

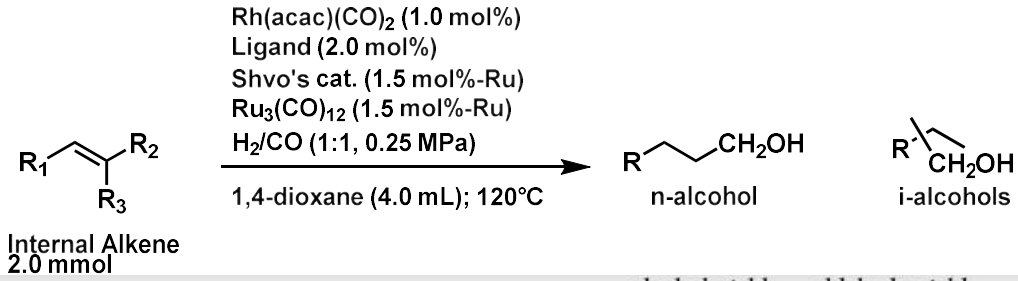
Yuki, Y.; Takahashi, K.; Tanaka, Y.; Nozaki, K. *J. Am. Chem. Soc.* **2013**, *135*, 17393.



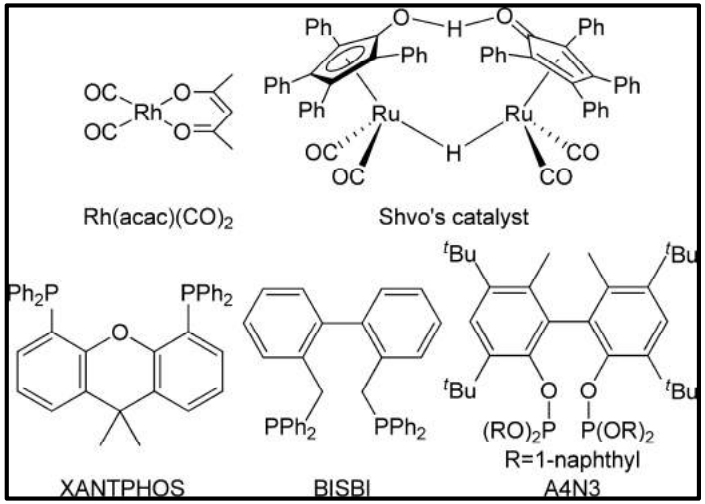
Seayad, A.; Ahmed, M.; Klein, H.; Jackstell, R.; Gross, T.; Beller, M. *Science* **2002**, *297*, 1676.

Behr, A.; Obst, D.; Schulte, C.; Schosser, T. *J. Mol. Catal. A: Chem.* **2003**, *206*, 179.

Reaction Optimization

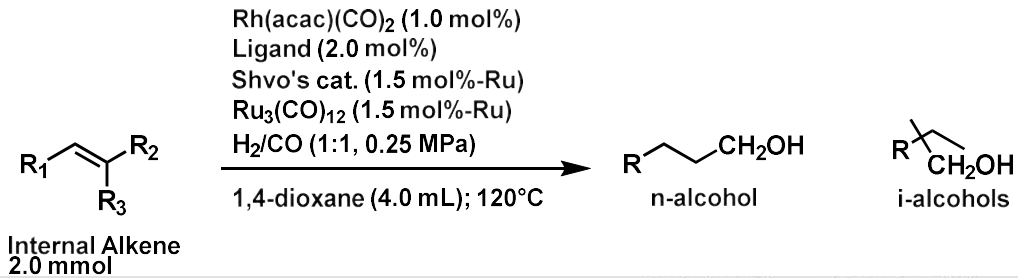


run	alkene	ligand	time (h)	conversn (%)	total n/i[b]	alcohol yield (%) n	alcohol yield (%) i[c]	aldehyde yield (%) n	aldehyde yield (%) i[d]	direct hydrogenation of C=C (%)	total others (%)[e]
1	(Z)-2-decene	PPh_3 (4.0 mol %)	36	47	0.8	4.8	8.1	11	13	nd[f]	1.0
2	(Z)-2-decene	$P(OPh)_3$ (4.0 mol %)	36	94	0.7	24	38	8.0	6.5	nd[f]	0.4
3	(Z)-2-decene	XANTPHOS	36	88	1.3	35	27	4.0	2.4	nd[f]	5.7
4	(Z)-2-decene	BISBI	36	42	0.4	6.0	19	2.6	4.0	6.0	trace
5	(Z)-2-decene	A4N3	36	99	18	75	4.2	3.5	0.2	4.8	trace



Yuki, Y.; Takahashi, K.; Tanaka, Y.; Nozaki, K. *J. Am. Chem. Soc.* **2013**, *135*, 17393.

Reaction Optimization



run	alkene	ligand	time (h)	conversn (%)	total n/i[b]	alcohol yield (%) n	alcohol yield (%) i[c]	aldehyde yield (%) n	aldehyde yield (%) i[d]	direct hydrogenation of C=C (%)	total others (%)[e]
1	(Z)-2-decene	PPh_3 (4.0 mol %)	36	47	0.8	4.8	8.1	11	13	nd[f]	1.0
2	(Z)-2-decene	$P(OPh)_3$ (4.0 mol %)	36	94	0.7	24	38	8.0	6.5	nd[f]	0.4
3	(Z)-2-decene	XANTPHOS	36	88	1.3	35	27	4.0	2.4	nd[f]	5.7
4	(Z)-2-decene	BISBI	36	42	0.4	6.0	19	2.6	4.0	6.0	trace
5	(Z)-2-decene	A4N3	36	99	18	75	4.2	3.5	0.2	4.8	trace
6	(Z)-2-tridecene	A4N3	36	100	12	83	7.1	trace	trace	6.7	2.6
7	1-octene	A4N3	18	100	40	24	0.6	59	1.5	5.5	4.4
8	(Z)-2-octene	A4N3	18	100	27	34	1.5	49	1.5	5.7	1.7
9	(E)-2-octene	A4N3	18	100	17	45	2.3	16	1.2	5.0	6.4
10	(E)-4-octene	A4N3	18	100	16	46	3.0	17	0.9	4.4	8.2
11	1-methylcyclohexene	A4N3	36	37[i]		trace	19	trace	trace	trace	6.3
12	2-methylstyrene (E:Z = 1.8:1.0)	A4N3	36	100[g]	4.9	69[g]	14	trace	trace	6.6[e]	7.7
13	(Z)-6-nonen-1-ol	A4N3	36	100[g]	9.3	62[h]	6.7	trace	trace	24[e]	5.0
14	(Z)-6-nonenyl acetate	A4N3	36	100[g]	4.6	65[g]	14	trace	trace	6.6[e]	12
15	methyl oleate	A4N3	36	86[g]	1.9	37[h]	19[g]	5.0[g]	3.0[g]	23[i]	nd[f]
16[k]	(Z)-2-decene	A4N3	36	100	23	71	3.1	1.0	trace	7.7	3.7
17[k]	methyl oleate	A4N3	36	93	4.4	53[h]	12[g]	trace	trace	29[i]	nd[f]

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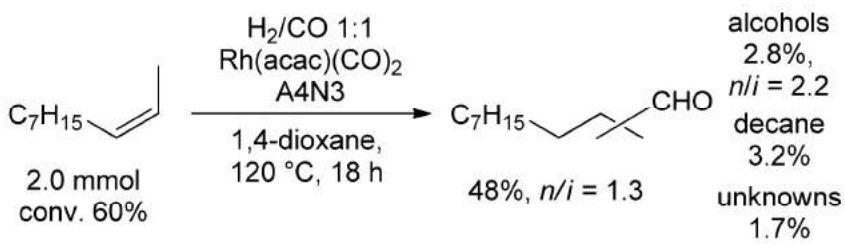
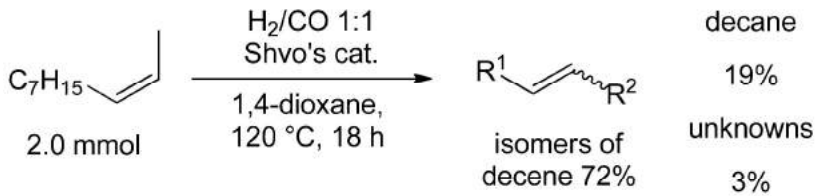
Control Experiments to Elucidate Catalyst Roles

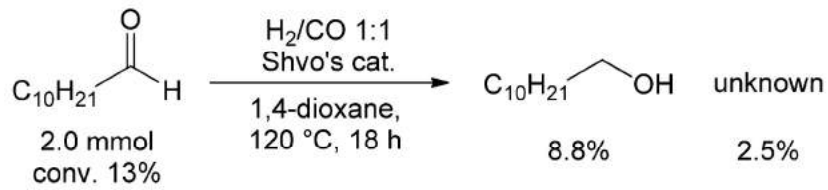
a) Isomerization/hydroformylation of (*Z*)-2-decene by Rh/A4N3



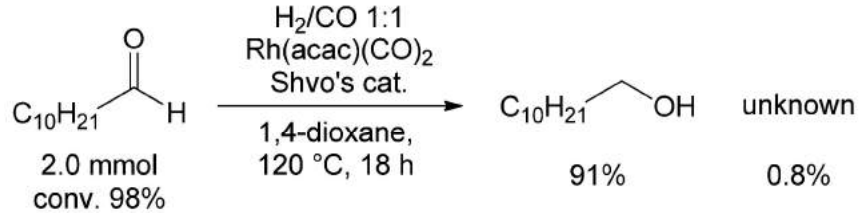
b) Isomerization of (*Z*)-2-decene by Shvo's catalyst



c) Hydrogenation of *n*-undecanal by Shvo's catalyst



d) Hydrogenation of aldehyde by $Rh(acac)(CO)_2$/Shvo's catalyst



Conditions: Substrate 2.0 mmol, 1,4-dioxane 4.0 mL, H_2 0.25 MPa, CO 0.25 MPa, 120 °C, 18 h. a) $Rh(acac)(CO)_2$ 1.0 mol%, A4N3 2.0 mol%. b), c) Shvo's catalyst 1.5 mol% (Ru). d) $Rh(acac)(CO)_2$ 1.0 mol%, Shvo's catalyst 1.5 mol% (Ru).

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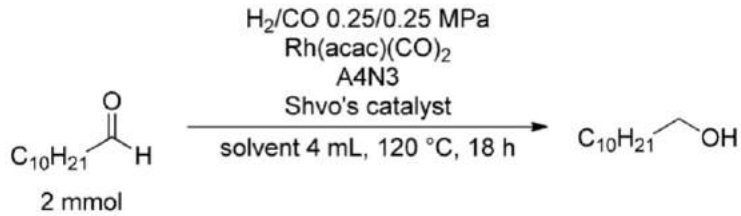
Hydrogenation Varying Catalyst Components



run	$Rh(acac)(CO)_2$ (mol %)	A4N3 (mol %)	Shvo's cat. (mol % (Ru))	conversn (%)	*n*-alcohol (%)	other deviations from run 1
1	0	0	2.0	13	8.8	
2	1.5	0	2.0	98	91	
3	1.5	2.0	2.0	96	85	
4	1.5	0	0	13	7.5	
5	0	2.0	2.0	22	7.9	
6	0	0	2.0	98	85	$[Rh(coe)_2Cl]_2$ 1.0 mol %
7	1.5	0	0	34	22	tetraphenylcyclopentadienone 1.0 mol %
8	1.5	0	0	35	8.2	$Ru_3(CO)_{12}$ 2.0 mol % (Ru)
9	0	0	2.0	91	79	DMA used as a solvent

[a]Conditions: undecanal 2.0 mmol, H_2 0.25 MPa, CO 0.25 MPa, 1,4-dioxane 4.0 mL, 120 °C, 18 h. Yields were determined by gas chromatography using dodecane as an internal standard.

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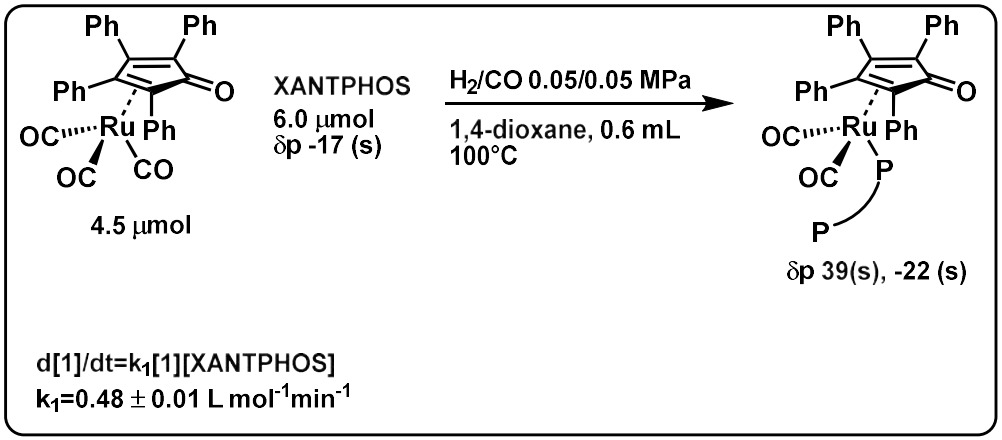
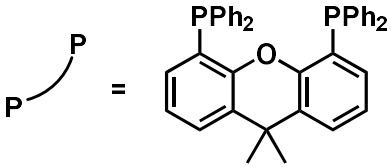
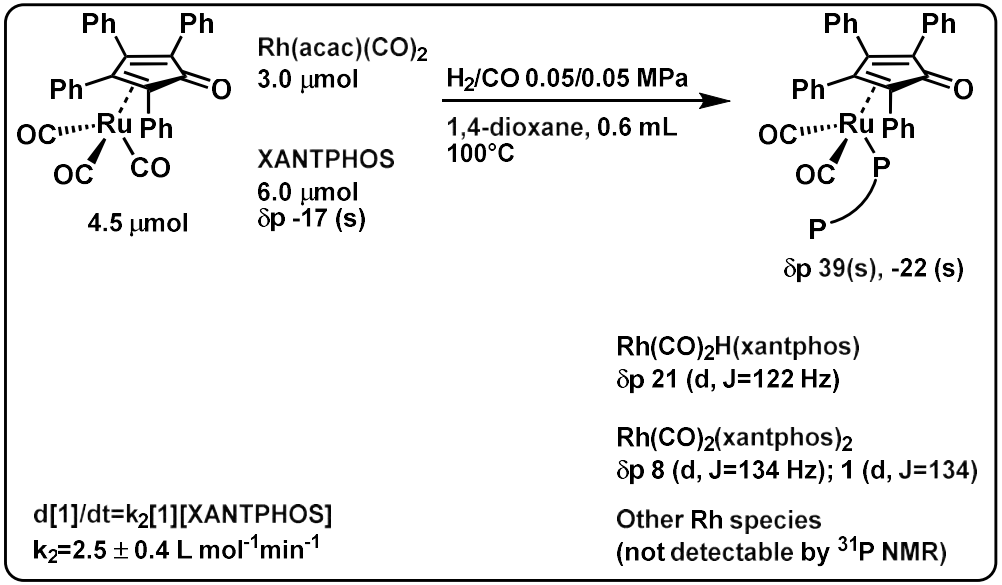
Kinetic Experiments



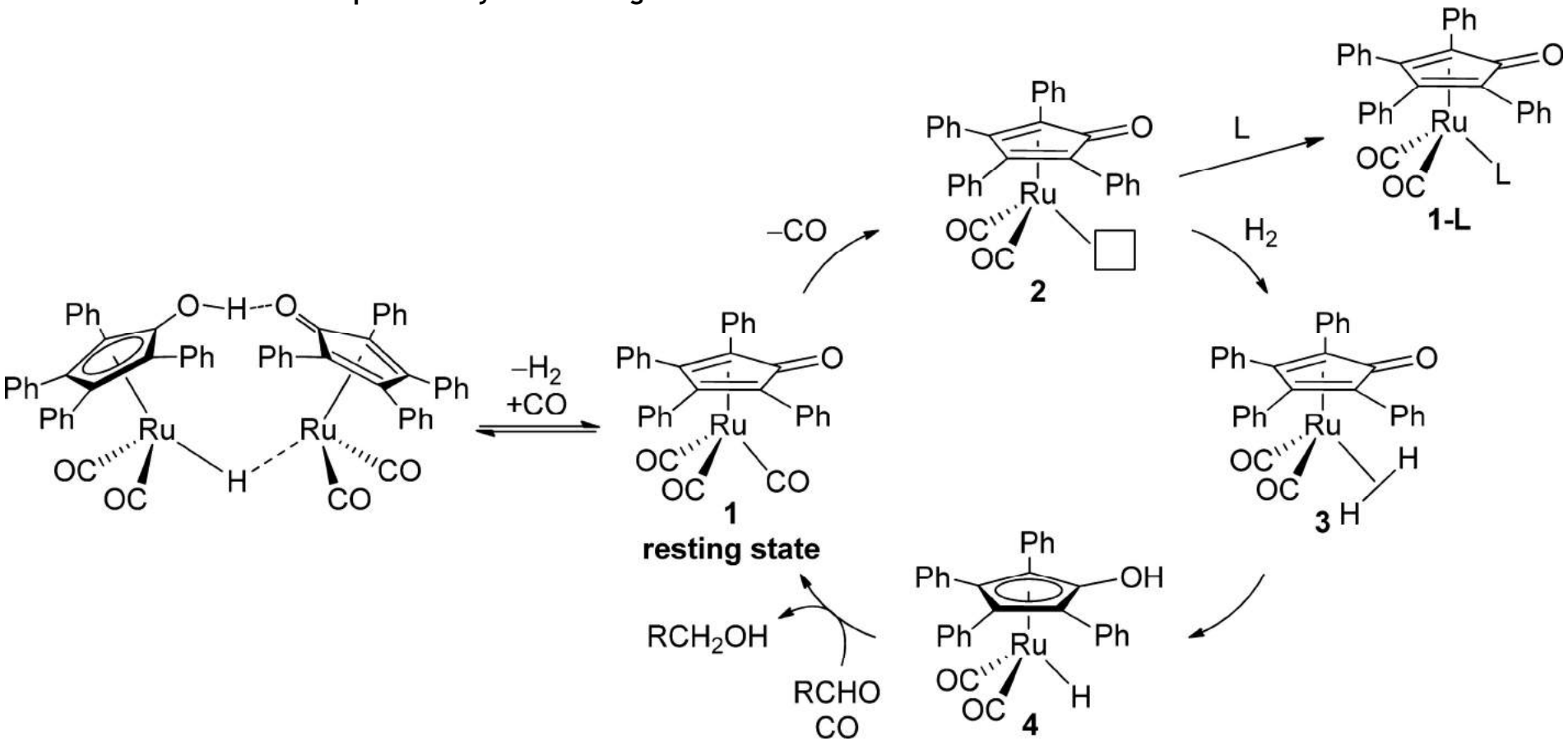




Yuki, Y.; Takahashi, K.; Tanaka, Y.; Nozaki, K. *J. Am. Chem. Soc.* **2013**, *135*, 17393.

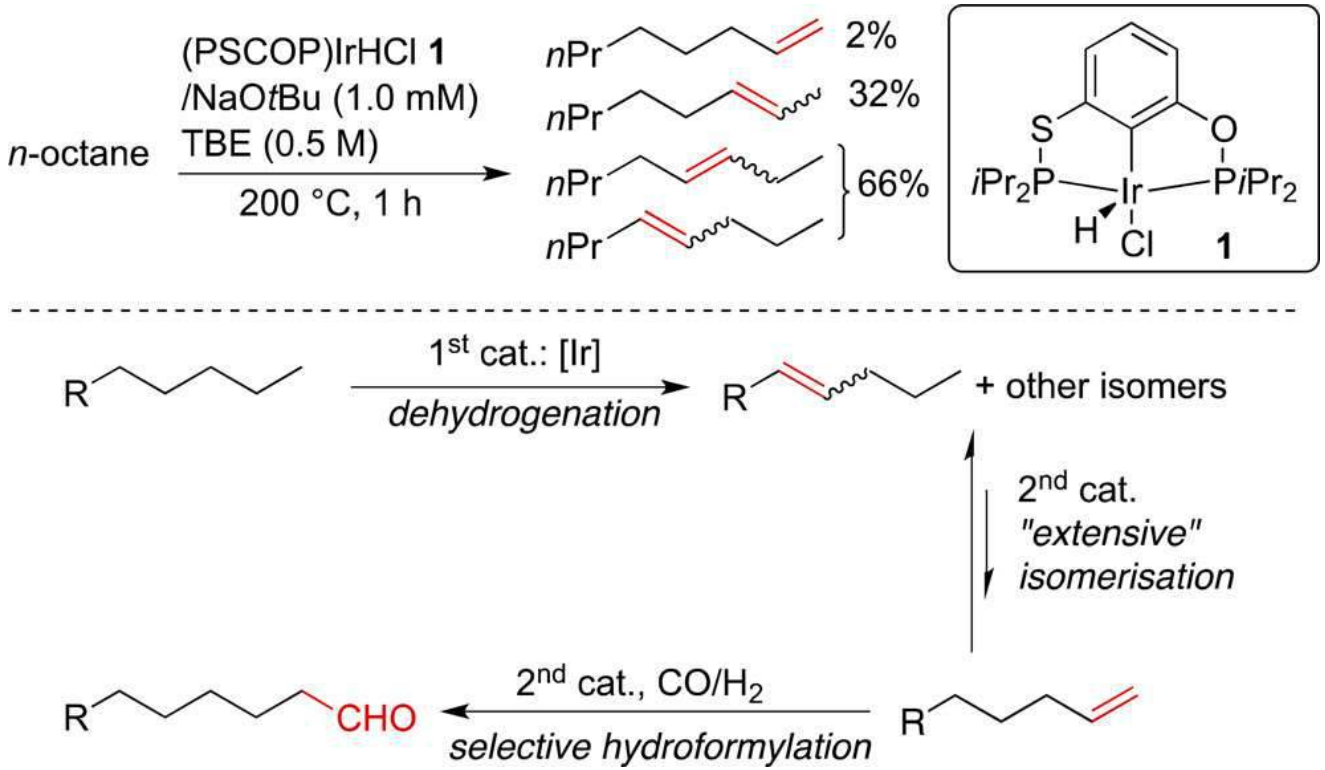
Proposed Hydrogenation Mechanism

Scheme 3. Proposed Reaction Mechanism of Hydrogenation of Aldehyde by Shvo's Catalyst under H_2/CO Pressure and Trap of Coordinative Unsaturated Species 2 by Another Ligand L.



Yuki, Y.; Takahashi, K.; Tanaka, Y.; Nozaki, K. *J. Am. Chem. Soc*. **2013**, *135*, 17393.

Functionalization from Alkanes



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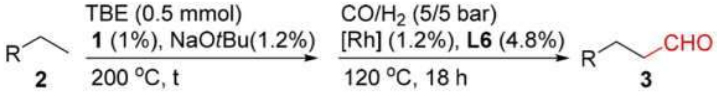
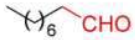
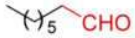
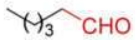
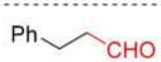
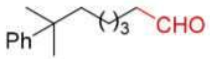
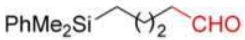
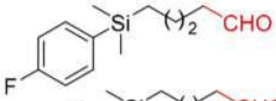
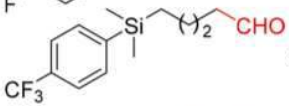
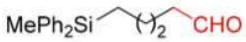
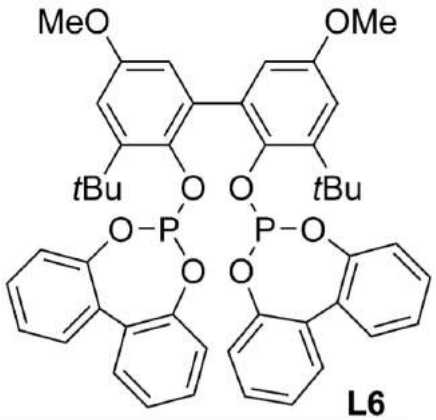
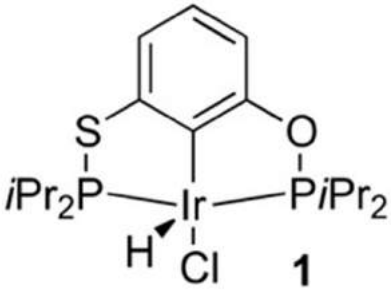
Functionalization from Alkanes



Entry	t (min)	Product		Yield (%)	*n*:*i*
1	10		**3a**	81(70)	13.9
2	10		**3b**	82(71)	12.5
3	10		**3c**	87(78)	11.6
4	10		**3d**	75(66)	8.5
5	30		**3e**	70(55)	19.6
6	30		**3f**	67	23.3
7[b]	30		**3g**	84	48.9
8[c,d]	300		**3h**	48	1.8
9[c,d]	300		**3i**	82	1.0
10[c,e]	180		**3j**	64(60)	10.6
11[c,e]	180		**3k**	82(67)	17.1
12[c,e]	180		**3l**	86(72)	18.3
13[c,e]	180		**3m**	64(54)	10.4
14[c,e]	180		**3n**	63(55)	11.3
15[c,e]	180		**3o**	78(73)	16.5

[a]Conditions: **1** (1% relative to TBE), NaO*t*Bu (1.2%), alkane (2 mL), [Rh] (1.2%), **L6**:[Rh] = 4:1. Yields and *n*:*i* ratios were determined by GC. Numbers in parentheses are isolated yields. Yields are relative to TBE. [b]At 190 °C for AD. [c]**1** (2 mol % relative to TBE), NaO*t*Bu (2.4 mol %). [d]Rh(acac)(CO)$_2$ (0.8 mol %) and **L6** (3.2 mol %), [e]Alkane (1.5 mmol), *p*-xylene (1.5 mL).





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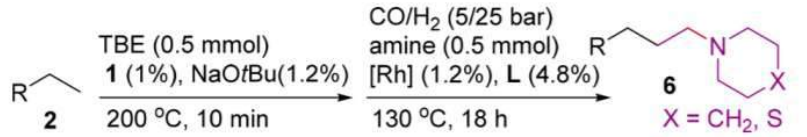
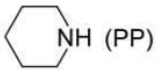
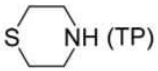
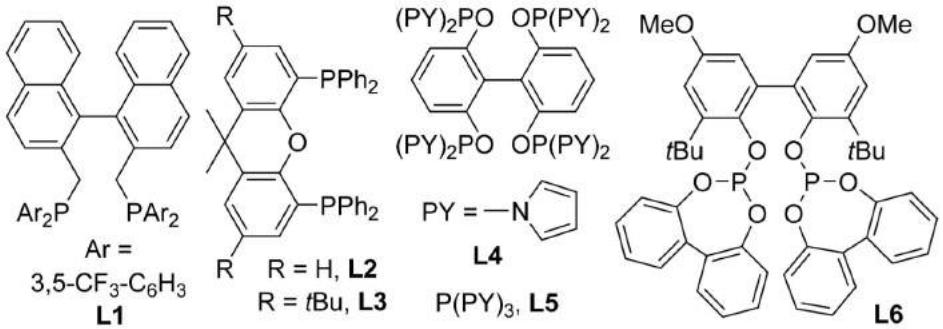
Functionalization from Alkanes



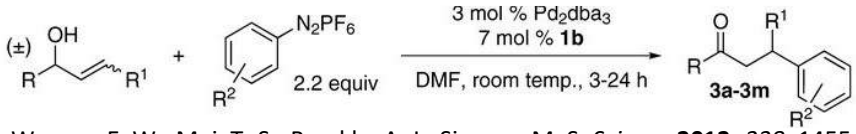
Entry	Alkane	L	Amine	Yield (%)	Amine selectivity (%)	*n*:*i*
1[b]	*n*-octane	**L6**	 NH (PP)	22	47	10.4
2[b]	*n*-octane	**L4**	PP	trace	-	-
3[c]	*n*-octane	**L5**	PP	59	93	0.4
4[c]	*n*-octane	**L2**	PP	20	22	0.3
5[b]	*n*-octane	**L1**	PP	58	96	1.6
6	*n*-octane	**L1**	PP	85	99	1.3
7	*n*-octane	**L1**	 NH (TP)	36	93	4.0
8[d]	*n*-heptane	**L1**	PP	75	99	3.3
9[d]	*n*-heptane	**L1**	TP	71	97	4.6
10[e]	*n*-pentane	**L1**	PP	95	98	6.1
11[e]	*n*-pentane	**L1**	TP	60	99	24.0

[a]Conditions: **1** (1 mol % relative to TBE), NaO*t*Bu (1.2 mol %), alkane (2 mL), [Rh] = $Rh(acac)(CO)_2$ (1.2 mol %), **L**:[Rh] = 4:1. Amine (0.5 mmol). Yields, amine selectivities, and *n*:*i* ratios were determined by GC. Yields are relative to TBE. [b]120 °C, CO/H_2 (10/50 bar) for ISO-HAM. [c]120 °C, CO/H_2 (5/33 bar) for ISO-HAM. [d]AD 200 °C, 30 min. [e]AD 190 °C, 30 min.

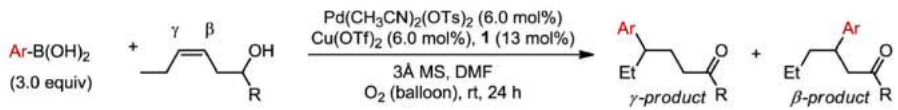


Tang, X; Jia, X.; Huang, Z. *J. Am. Chem. Soc.* **2018**, *140*, 4157.

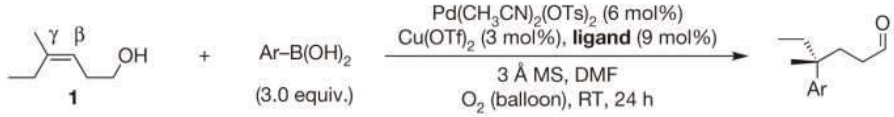
Redox-Relay Strategy



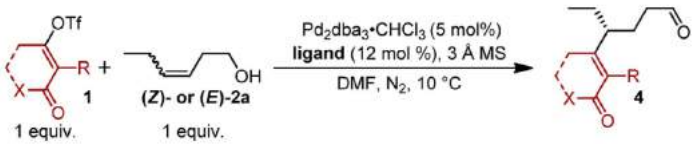
Werner, E. W.; Mei, T.-S.; Burckle, A. J.; Sigman, M. S. *Science* **2012**, *338*, 1455.



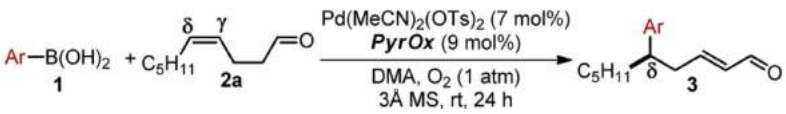
Mei, T.-S.; Werner, E. W.; Burckle, A. J.; Sigman, M. S. *J. Am. Chem. Soc*. **2013**, *135*, 6830.



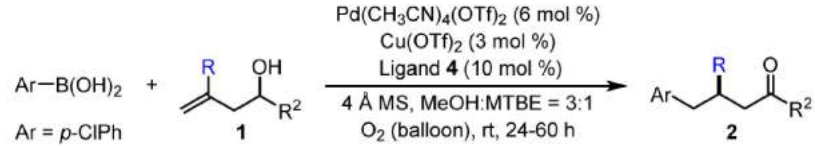
Mei, T.-S.; Patel, H. H.; Sigman, M. S. *Nature* **2014***, 508*, 340.



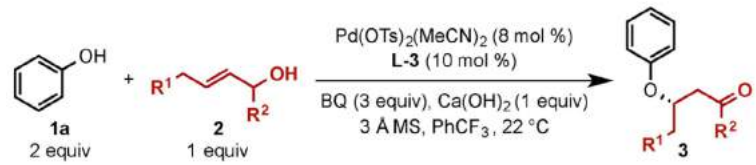
Patel, H. H.; Sigman, M. S. *J. Am. Chem. Soc*. **2015**, *137*, 3462.



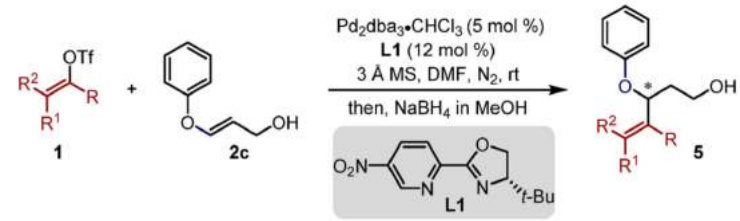
Zhang, C.; Santiago, C. B.; Kou, L.; Sigman, M. S. *J. Am. Chem. Soc*. **2015**, *137*, 7290.



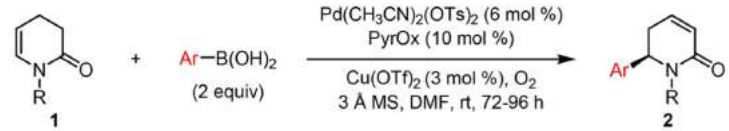
Chen, Z. M.; Hilton, M. J.; Sigman, M. S. *J. Am. Chem. Soc*. **2016**, *138*, 11461.



Race, N. J.; Schwalm, C. S.; Nakamuro, T.; Sigman, M. S. *J. Am. Chem. Soc.* **2016**, *138*, 15881.

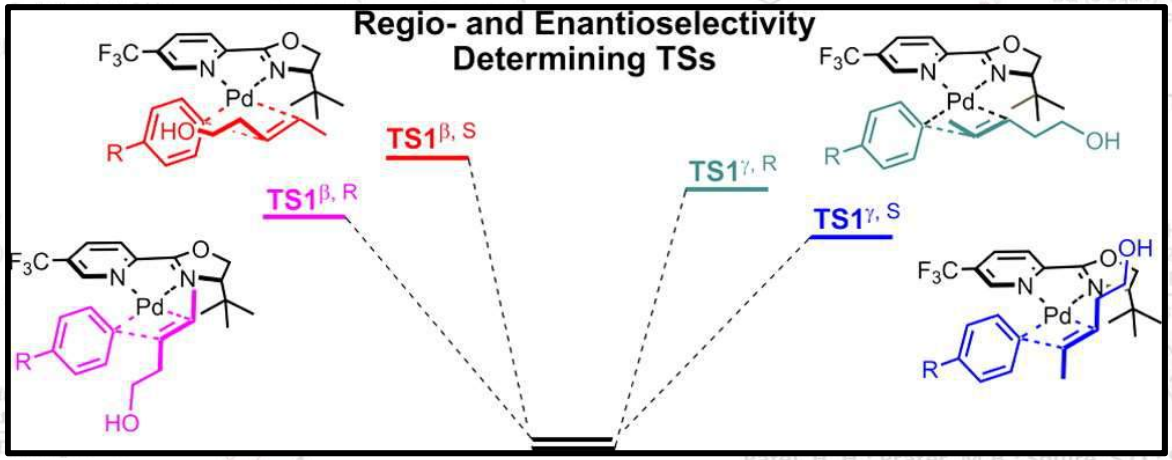


Patel, H. H.; Prater, M.B.; Squire, S.O.; Sigman, M. S. *J. Am. Chem. Soc.* **2018**, *140*, 5895.



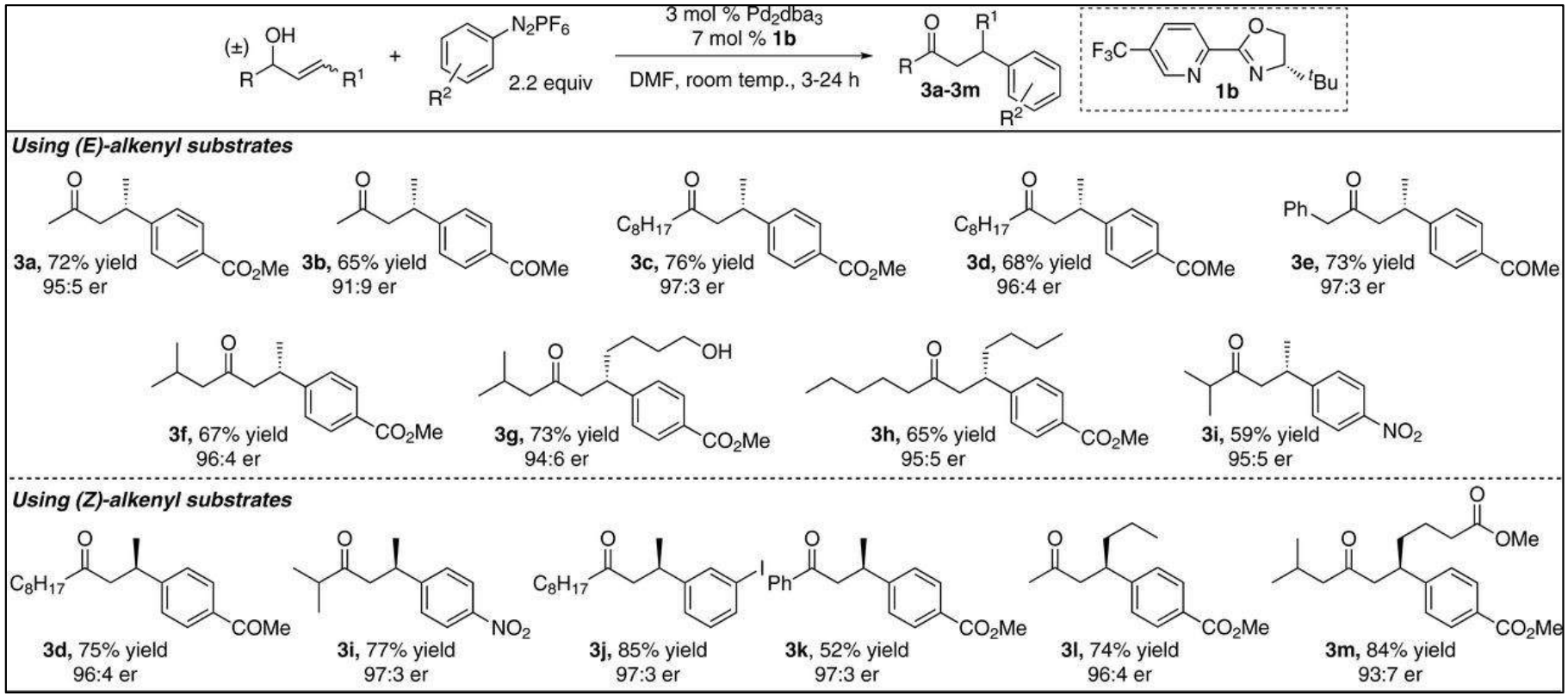
Yuan, Q.; Sigman, M. S. *J. Am. Chem. Soc***. 2018** ASAP

Redox-Relay Strategy



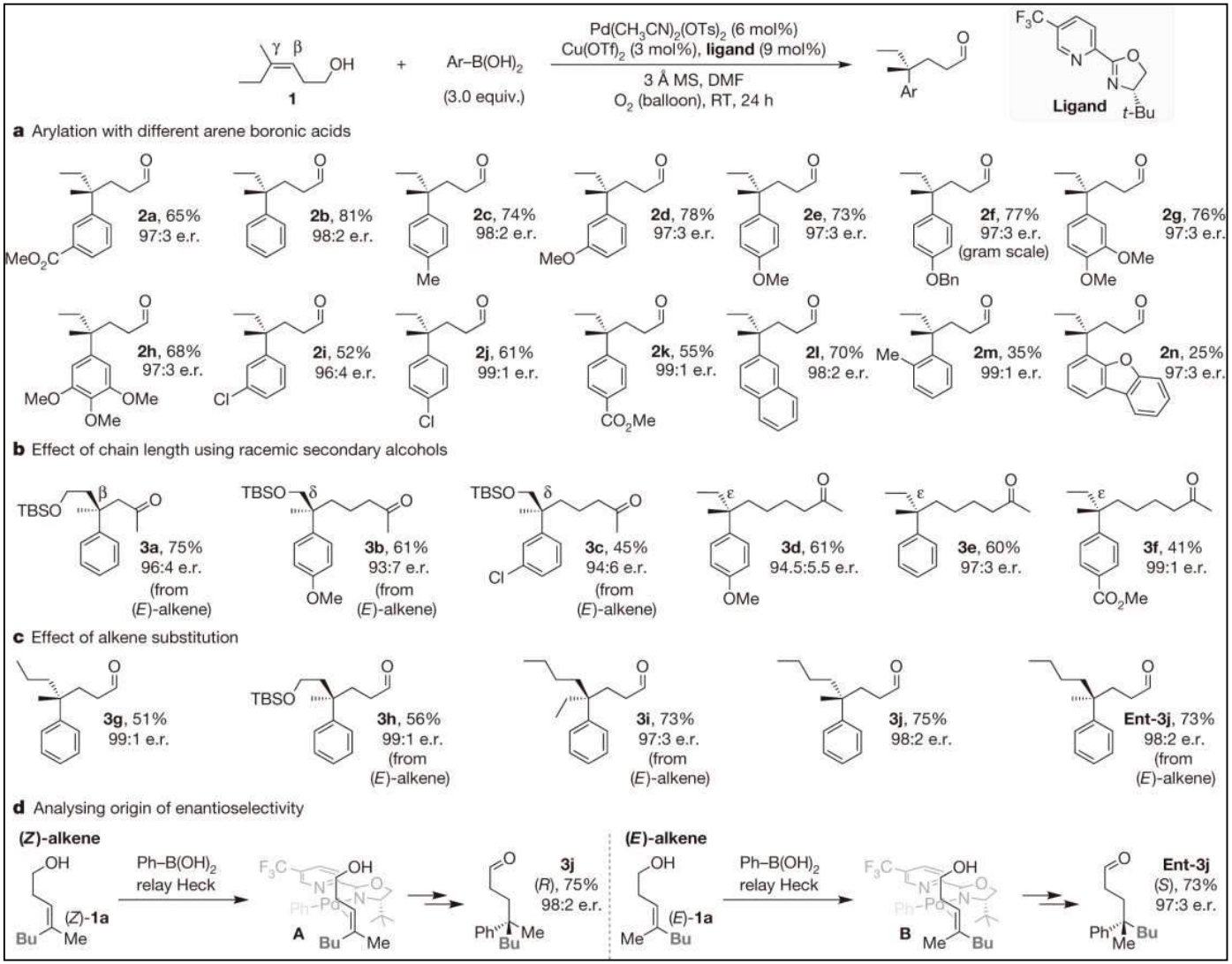
Xu, L.; Hilton, M. J.; Zhang, X.; Norrby, P. O.; Wu, Y. D.; Sigman, M. S.; Wiest, O. *J. Am. Chem. Soc.* **2014**, *136*, 1960.

Seminal Sigman Publication



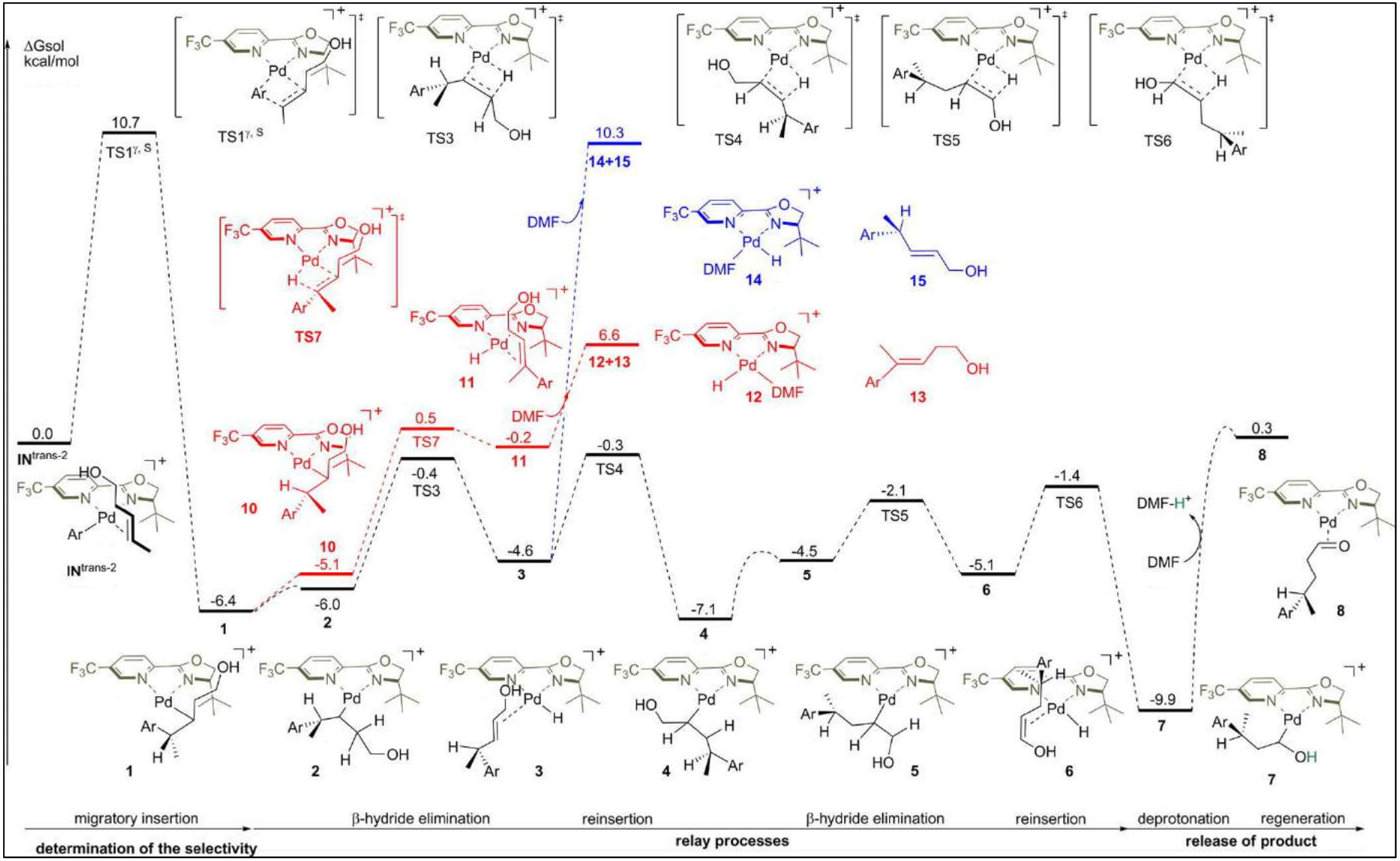
Werner, E. W.; Mei, T.-S.; Burckle, A. J.; Sigman, M. S. *Science* **2012**, *338*, 1455.

Quaternary Centers



Mei, T.-S.; Patel, H. H.; Sigman, M. S. *Nature* **2014**, *508*, 340.

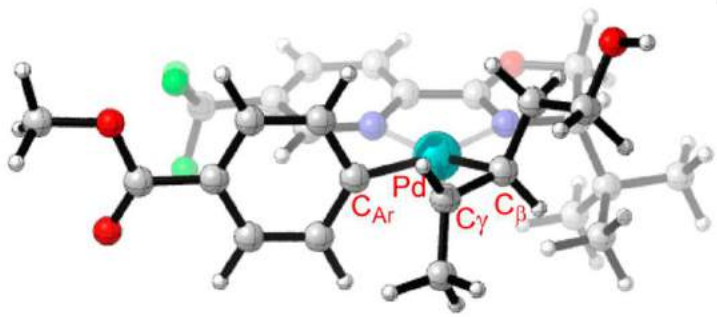
Computational Investigation



Xu, L.; Hilton, M. J.; Zhang, X.; Norrby, P. O.; Wu, Y. D.; Sigman, M. S.; Wiest, O. *J. Am. Chem. Soc.* **2014**, *136,* 1960

Computational Investigation

Table 2. NBO Charges and Key Dihedral Angles in TS1 and TS2

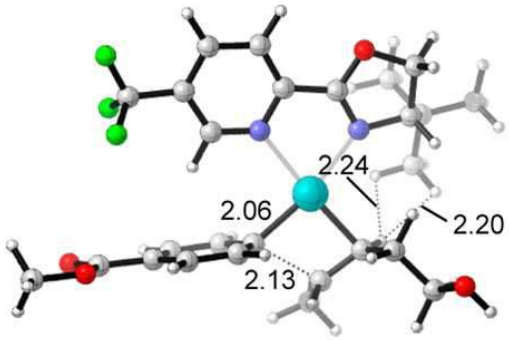


	TS1 $^{\gamma,S}$	TS1$^{\beta,R}$	TS2$^{\gamma,R}$	TS2$^{\beta,S}$
charge CH_{β}	0.00	0.11	−0.02	0.12
charge CH_{γ}	0.12	0.01	0.13	−0.01
C_{Ar}–Pd–C_{β}–C_{γ}	11.1°	15.5°	−16.3°	−17.8°

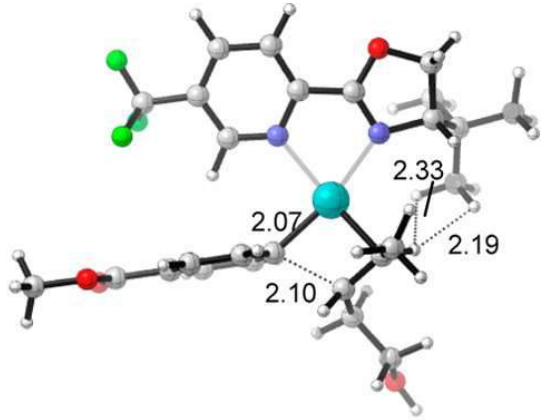
- "An NBO charge analysis indicates that, in the isomers of **TS1**, the alkene carbon forming a bond to Pd is substantially more negative than the carbon forming the bond to the aryl moiety. This negative charge can interact favorably with the positive charge of the oxygen-bound carbon in the γ-isomers of the TS, but not in the ß-isomers."

Xu, L.; Hilton, M. J.; Zhang, X.; Norrby, P. O.; Wu, Y. D.; Sigman, M. S.; Wiest, O. *J. Am. Chem. Soc.* **2014**, *136*, 1960

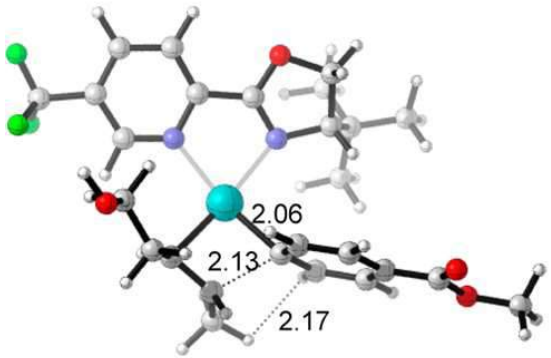
Computational Investigation



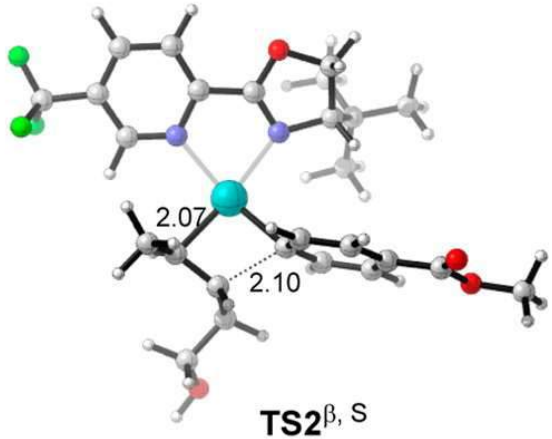
TS1$^{\gamma, S}$
$\Delta G^{\ddagger}$ = 10.7 kcal/mol



TS1$^{\beta, R}$
$\Delta G^{\ddagger}$ = 11.7 kcal/mol



TS2$^{\gamma, R}$
$\Delta G^{\ddagger}$ = 13.0 kcal/mol

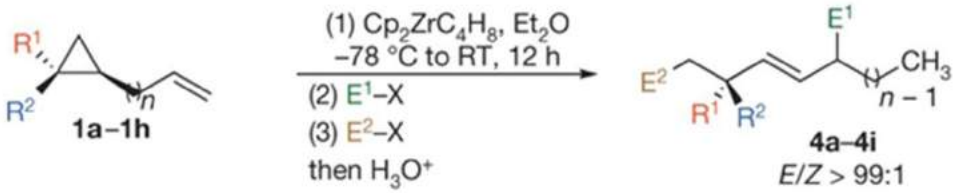


TS2$^{\beta, S}$
$\Delta G^{\ddagger}$ = 13.4 kcal/mol

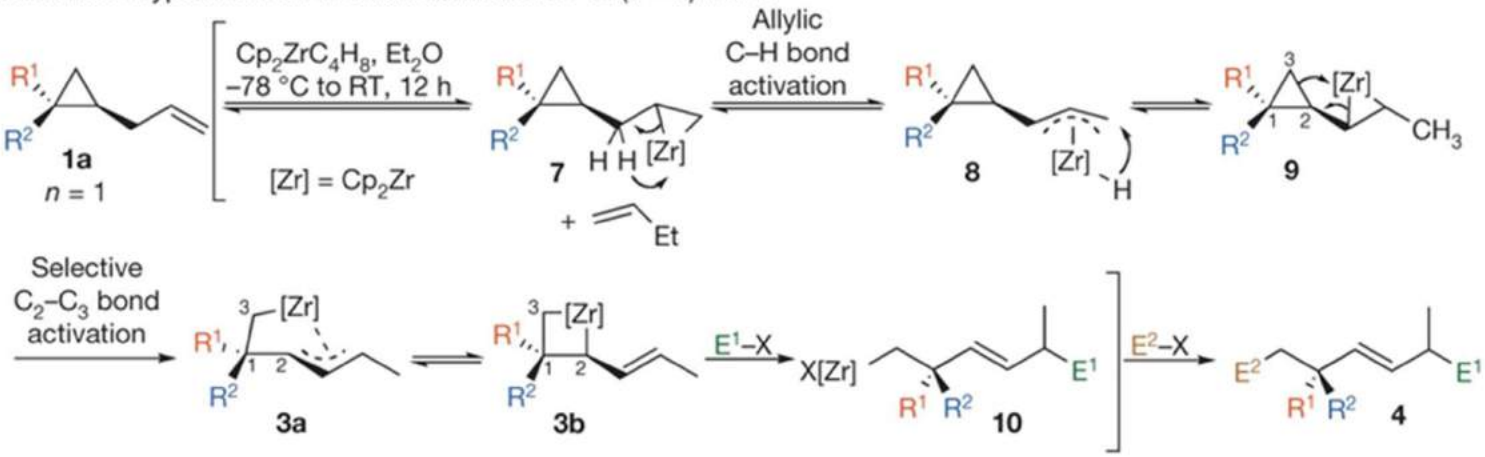
Xu, L.; Hilton, M. J.; Zhang, X.; Norrby, P. O.; Wu, Y. D.; Sigman, M. S.; Wiest, O. *J. Am. Chem. Soc.* **2014**, *136*, 1960

Presentation Overview

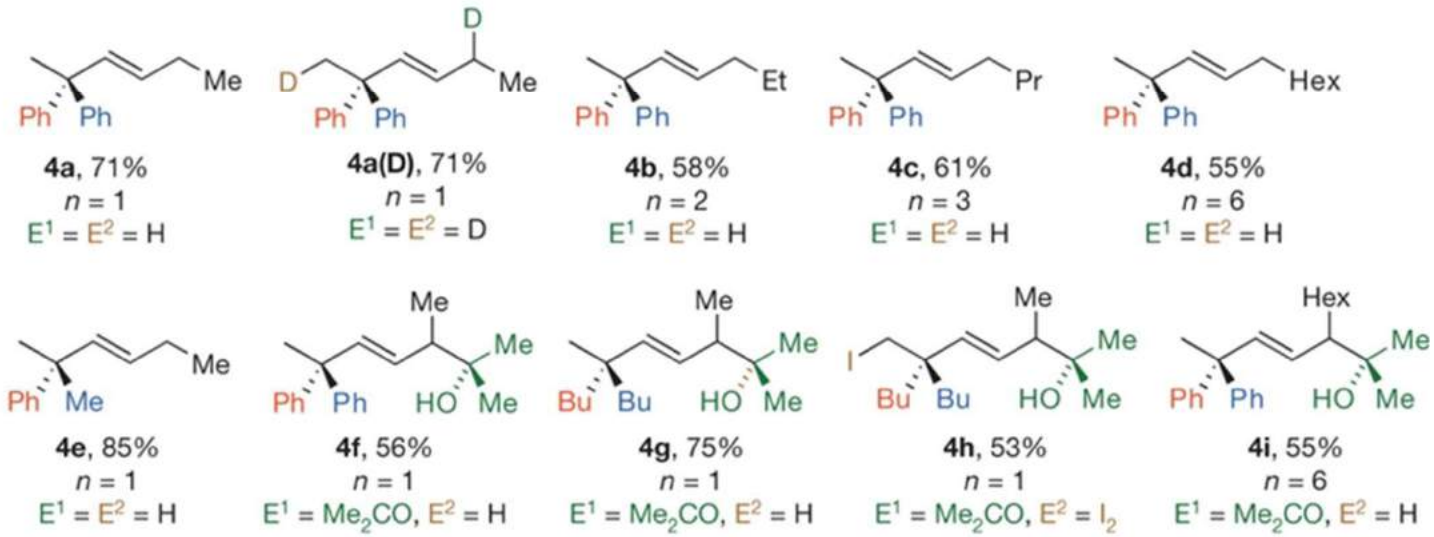
- Definition of remote functionalization and brief historical perspective.
- Historical development of metal-mediated chain walking processes and mechanistic paradigms.
- Survey 1,2-hydrogen shift processes from the literature as well as mechanistic investigations.
- **Survey 1,3-hydrogen shift processes from the literature.**
- Future directions and concluding remarks.



Mechanistic hypothesis for the transformation of **1a** (n = 1) into **4**

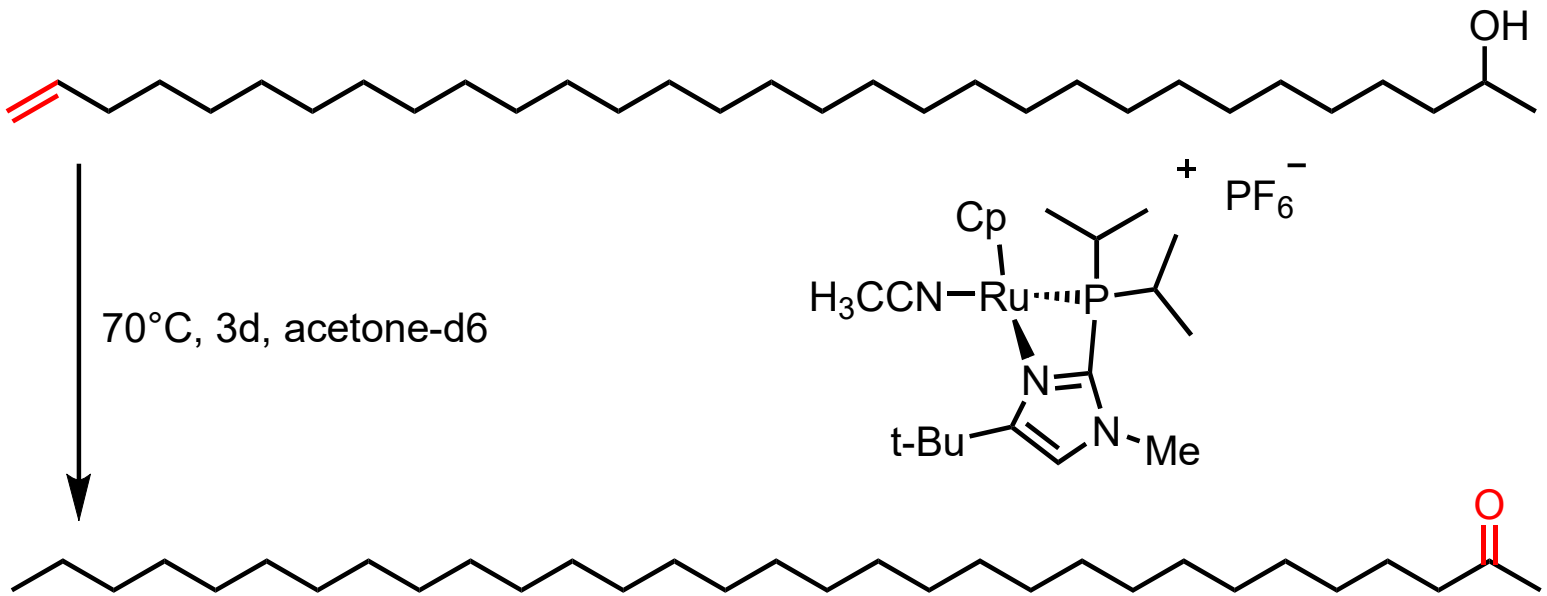


Representative examples



Masarwa, A.; Didier, D.; Zabrodski, T.; Schinkel, M.; Ackermann, L.; Marek, I. *Nature* **2014**, *505*, 199.

1-3, Long Range Champion



81%

Grotjahn, D. B.; Larsen, C. R.; Gustafson, J. L.; Nair, R.; Sharma, A. *J. Am. Chem. Soc.* **2007**, *129*, 9592.

Concluding Remarks

- Use of chain-walking enables novel synthetic strategies that should continue to be explored.
- Future developments should place emphasis on those methods which expand the scope beyond olefinic substrates.
- Enantioselective convergent strategies should become a priority.

- Questions?