Transfer hydrocyanation of alkenes and alkynes

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Supervisor: Dr. Zhangjie Shi

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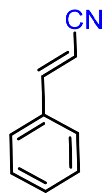
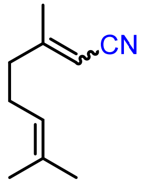
- Shuttle catalysis
- Transfer hydrocyanation

The application of nitriles

香料



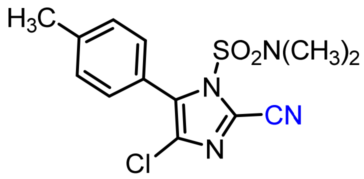
肉桂腈



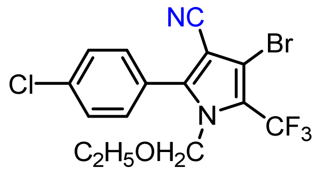
柠檬腈

Keller, W. et al. *Ber. Dtsch. Chem. Ges* **1932**, *65*, 1677.

农药



氯霜唑

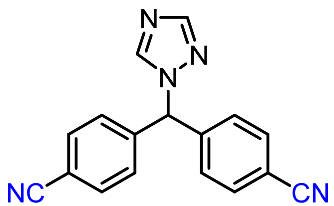


AC30360

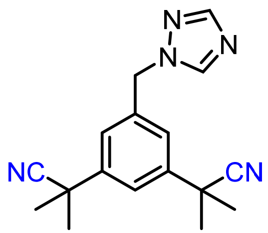
Froberger, C. F. et al. *J. Org. Chem*. **1957**, *22*, 1050.

Djandjighian, L. et al. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 6213.

医药



来曲唑

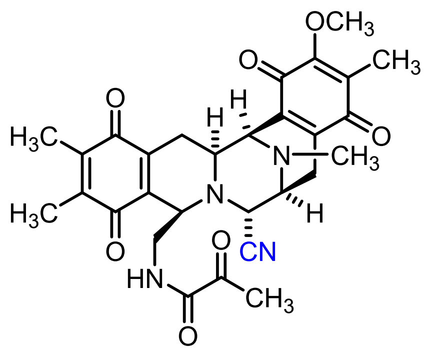


阿那曲唑

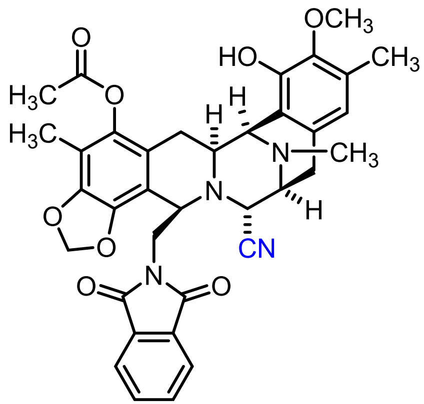
Bleasdale, J. E. et al. *J. Med. Chem*. **2002**, *45*, 1785.

Sanno, Y. et al. *J. Med. Chem*. **1977**, *20*, 141.

天然产物



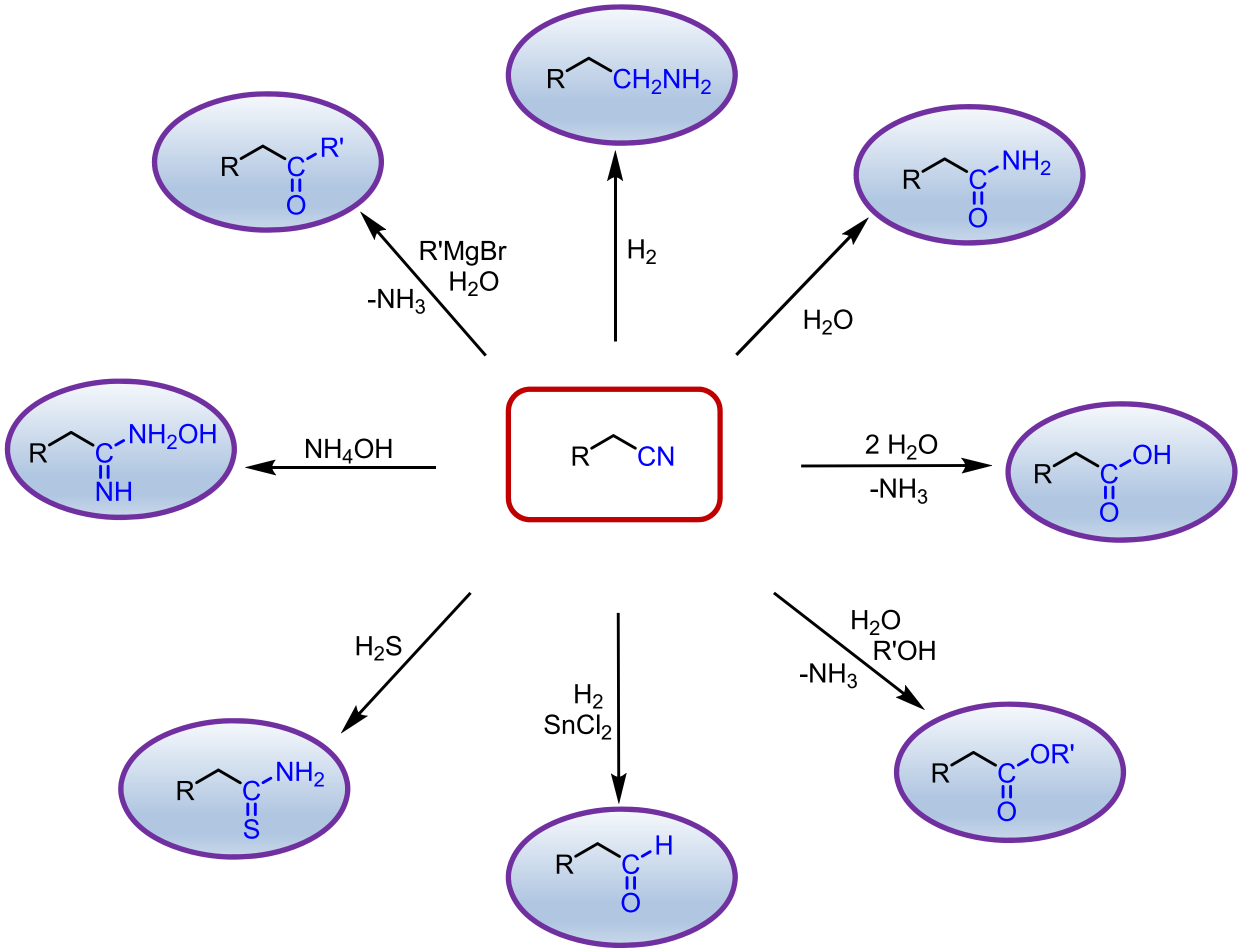
番红霉素A



Et-743

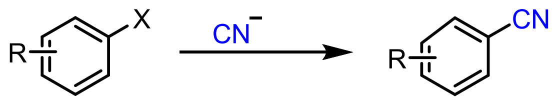
Corey, E. J. et al. *Org. Lett*. **1999**, 1, 75.

The derivatives of nitriles



Vogt, D. et al. *ChemCatChem* **2010**, *2*, 590.

The synthesis of nitriles

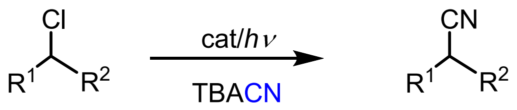


X = I, Br, Cl, OMs, OTs

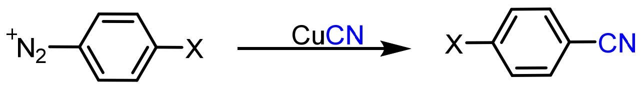
Lee, J. B. et al. *J. Org. Chem*. **1967**, *32*, 855.

Chatani, T. et al. *J. Org. Chem*. **1986**, *51*, 4714.

Rice, K. C. et al. *Tetrahedron. Lett*. **1998**, *39*, 2907.

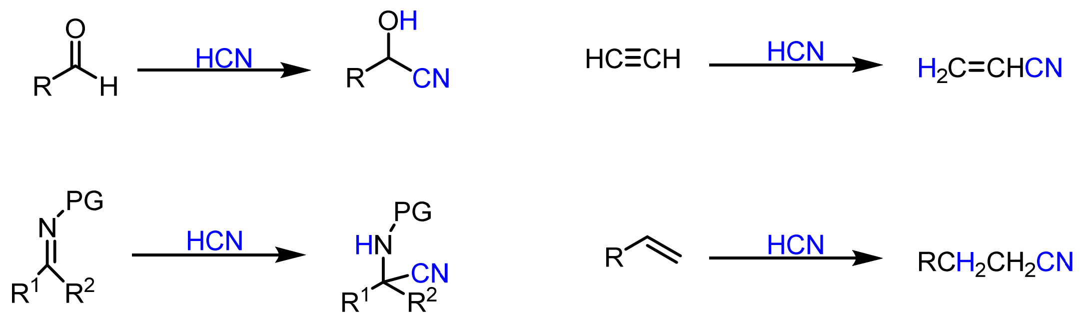


Peters, J. C. et al. *J. Am. Chem. Soc*. **2015**, *137*, 13902.



Petrovskii, P. V. et al. *J. Organomet. Chem*. **2004**, *689*, 3810.

The synthesis of nitriles

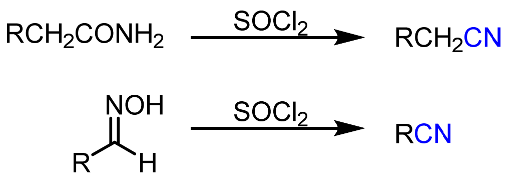


Choudary, B. M. et al. *Tetrahedron*. **2008**, *64*, 3351.

Otaka, K. et al. *J. Org. Chem*. **1991**, *56*, 6740.

Inoue, S. et al. *J. Am. Chem. Soc*. **1992**, *114*, 7965.

Liu, Y. H. et al. *J. Am. Chem. Soc.* **2018**, *140*, 7385.



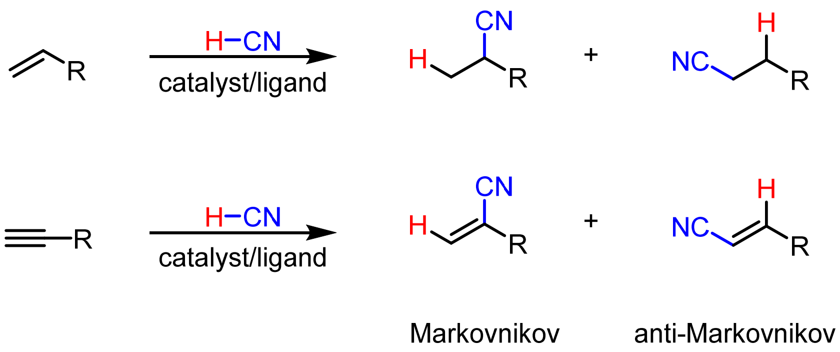
Akamanchi, K. G. et al. *J. Org. Chem*. **2007**, *72*, 662.

Mizuno, N. et al. *Angew. Chem. Int. Ed*. **2007**, *46*, 3922.

$$C_6H_5CH_3 + NH_3 \xrightarrow[O_2]{cat} C_6H_5CN$$

Mowry, D. F. et al. *Chem. Rev*. **1948**, *42*, 189.

Traditional hydrocyanation of alkenes and alkynes



HCN: Toxicity!

Corrosive!

Explosive!

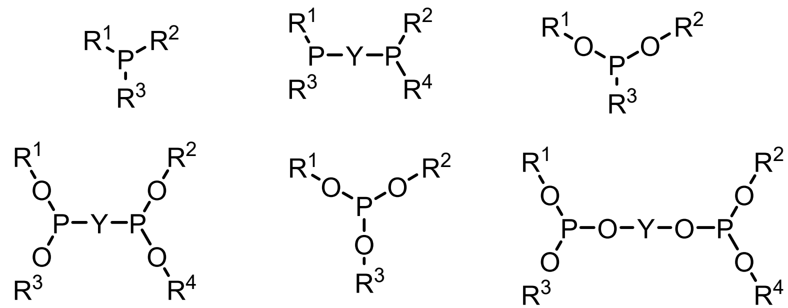
Poor selectivity!

Vogt, D. et al. *Chem. Commun.* **2010**, *46*, 8325.
Jacobsen, E. J. et al. *J. Am. Chem. Soc.* **2008**, *130*, 12594.

Metal

钴 Co	镍 Ni	铜 Cu
铑 Rh	钯 Pd	汞 Hg

Ligand



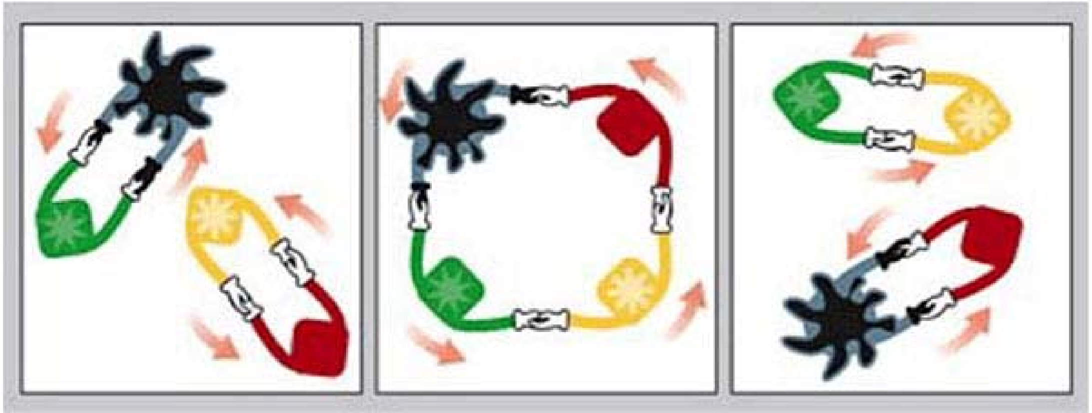
New strategy for hydrocyanation of alkenes and alkynes

Alkene metathesis

Richard Schrock

Robert H. Grubbs

Yves Chauvin



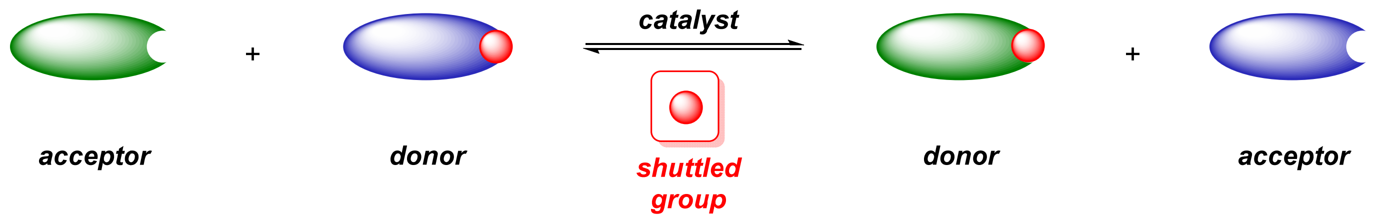
Chauvin, Y. et al. *Makromol Chem*, **1971**, *141,* 161.

Schrock, R. et al. *J. Am. Chem. Soc.* **1981**, *103*, 1440.

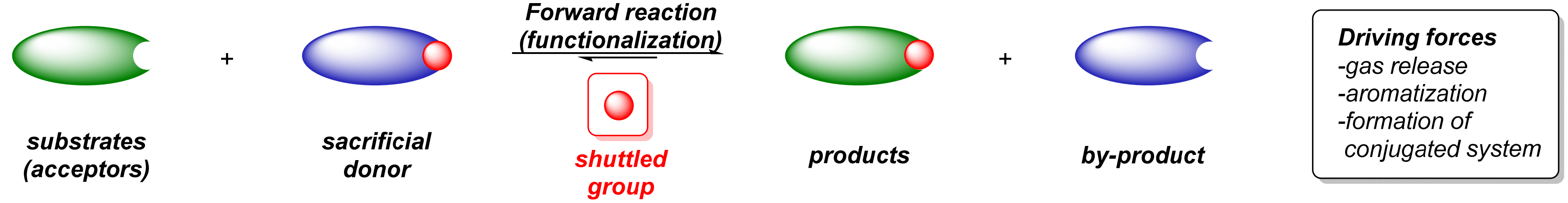
Grubbs, R. H. et al. *J. Am. Chem. Soc. 1992, 114,* 3974.

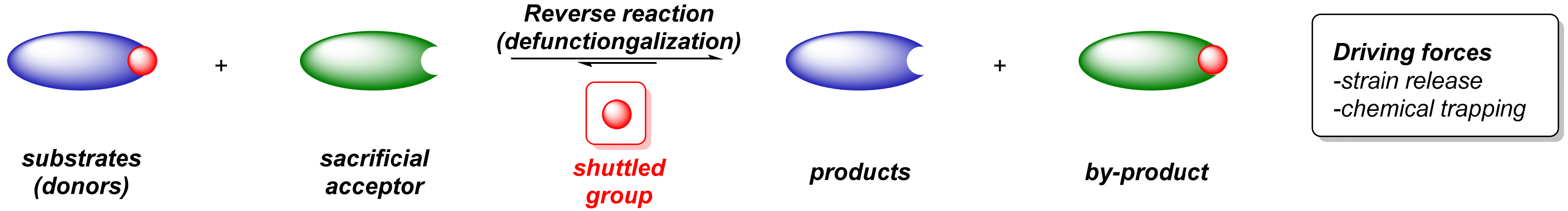
New strategy for hydrocyanation of alkenes and alkynes

Shuttle Catalysis



Morandi, B. et al. *ACS Catal*. **2016**, *6*, 7528.

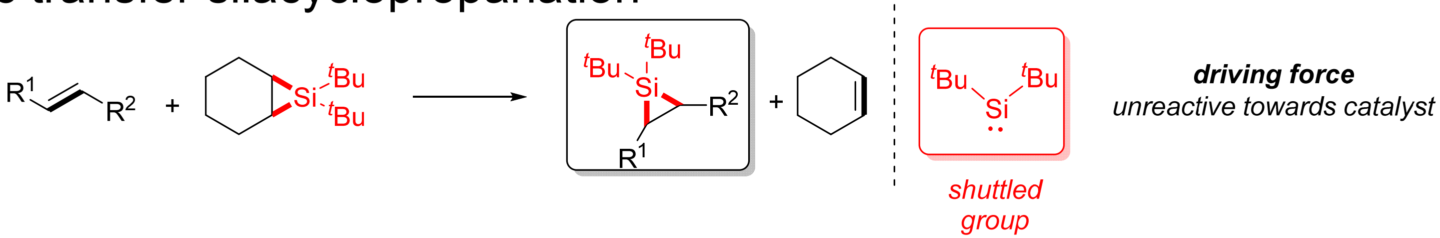




Morandi, B. et al. *ACS Catal*. **2016**, *6*, 7528.

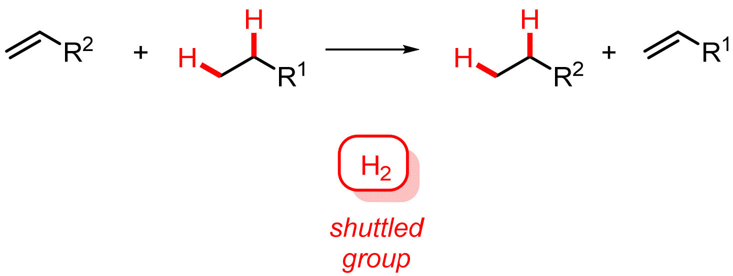
The examples of shuttle catalysis

Catalytic transfer silacyclopropanation



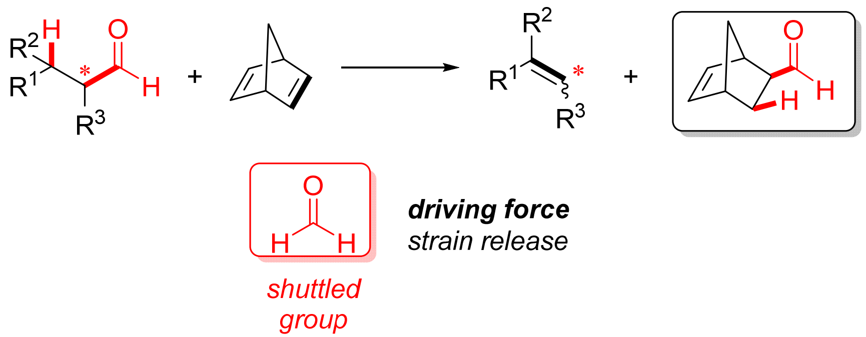
Driver, T. G. et al. *J. Am. Chem. Soc.* **2003**, *125*, 10659.

Catalytic transfer hydrogenation



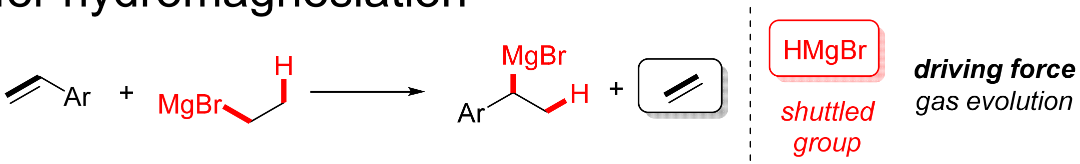
Wang, D. et al. *Chem. Rev.* **2015**, *115*, 6621.

Catalytic transfer hydroacylation



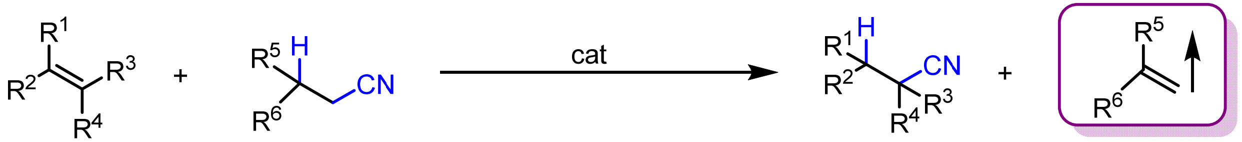
Murphy, S. K. et al. Science **2015**, *347*, 56.

Catalytic transfer hydromagnesiation



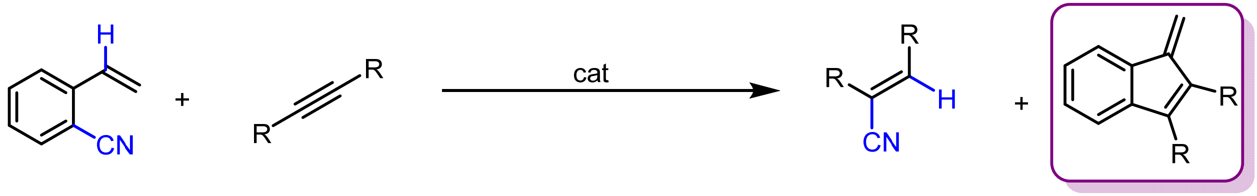
Greenhalgh, M. D. et al. *J. Am. Chem. Soc.* **2012**, *134*, 11900.

Hydrogen cyanide as shuttle catalysis



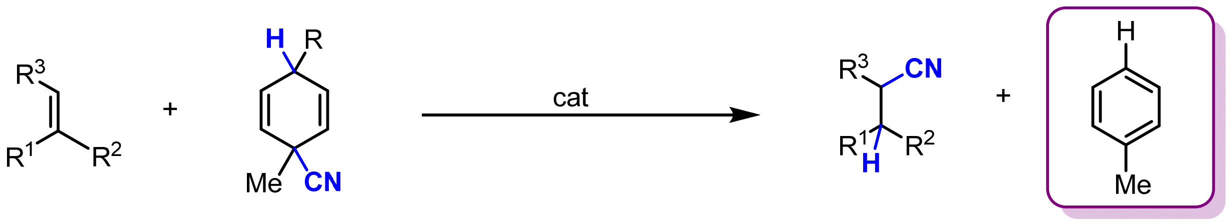
driving froce
gas evolution

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



driving froce
formation of conjugated system

Morandi, B. et al. *Chem. Eur. J.* **2016**, *22*, 15629.

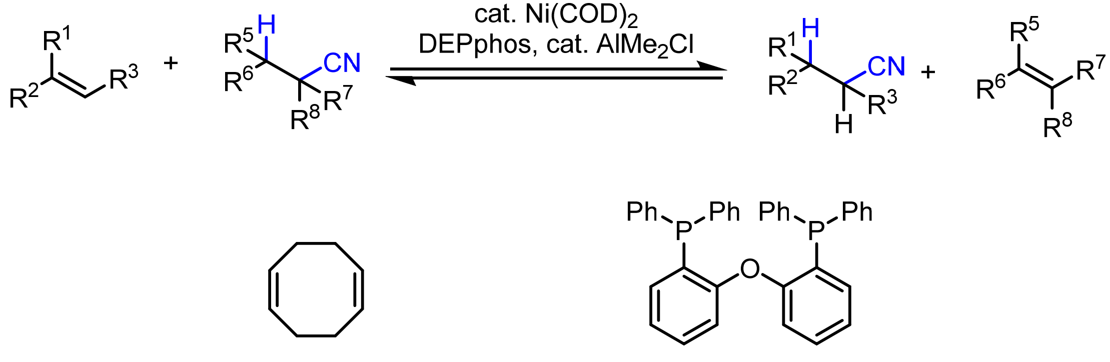


driving froce
aromatization

Studer, A. et al. *J. Am. Chem. Soc*. **2018**, *140*, 16353.

Oestreich, M. et al. *Angew. Chem. Int. Ed*. **2019**, *58*, 3579.

Catalytic reversible alkene-nitrile interconversion through controllable transfer hydrocyanation



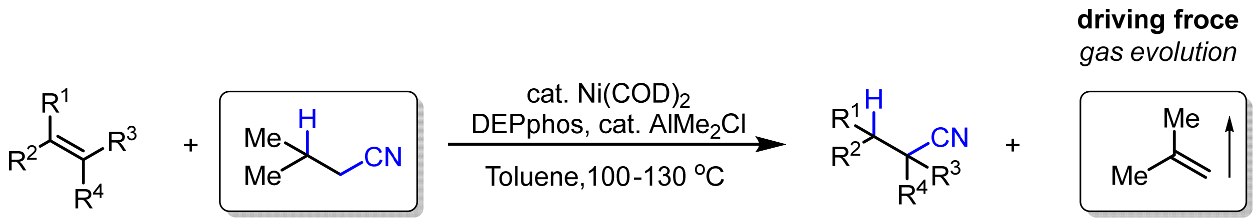
COD DPEphos

No HCN!
Reversible!
Anti-Markovnikov selectivity!
Broad subtrate scope (60 examples)!

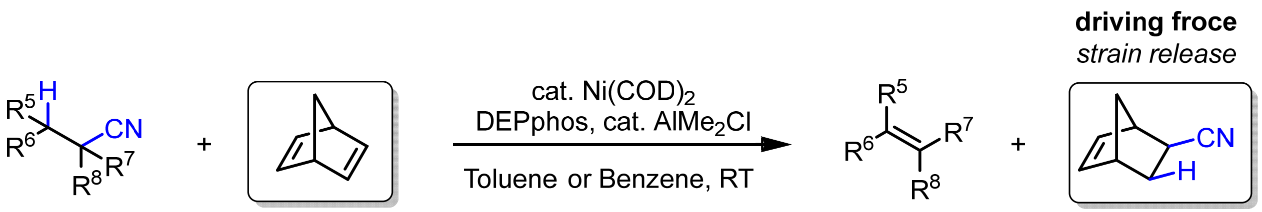
Morandi, B. et al. *Science* **2016**, *351*, 832.

Reversible transfer hydrocyanation of nitriles and alkenes

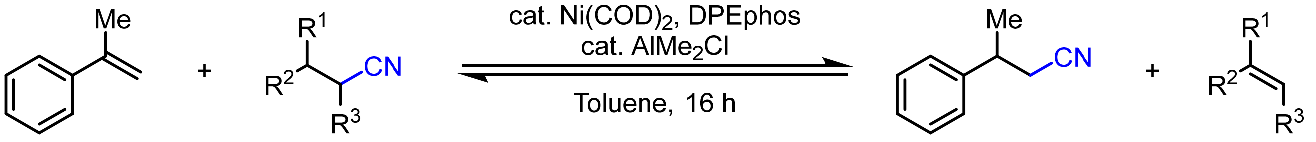
Catalytic Transfer Hydrocyanation (forward reaction)



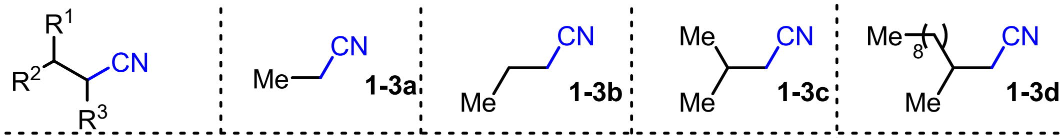
Catalytic Retro-Hydrocyanation (reverse reaction)



Selective manipulation of the alkene/nitrile equilibrium

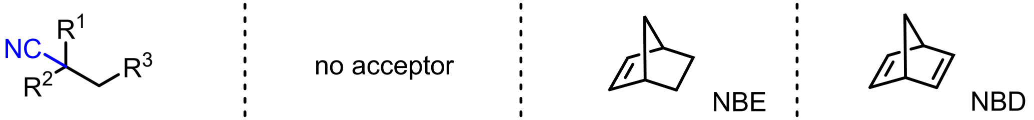


Hydrocyanation



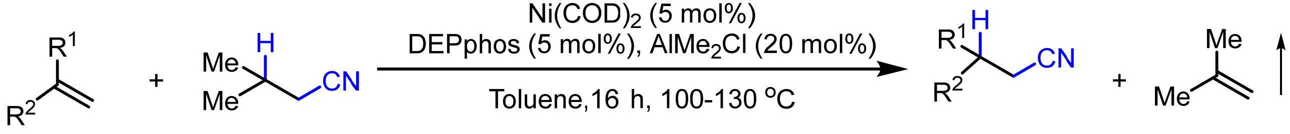
	1-3a	1-3b	1-3c	1-3d
yield (100 ^{o}C)	3%	26%	69%	60%
open system	—	41%	86%	67%

Retro-Hydrocyanation



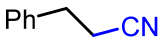
	no acceptor	NBE	NBD
yield (28 ^{o}C)	<5%	46%	99%

Exploration of hydrocyanation substrate scope

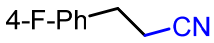


1-1 **1-2c** **1-3** **1-4c**

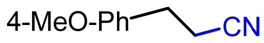
Aromatics



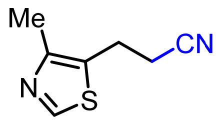
1-3e 86% (81:19)



1-3f 91% (83:17)

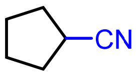


1-3g 93% (79:21)

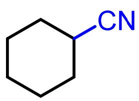


1-3h 71% (88:12)

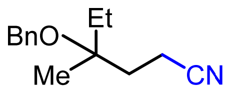
Aliphatics



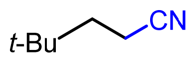
1-3i 83%



1-3j 91%

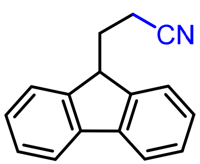


1-3k 79% (>95:5)

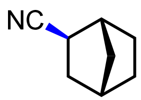


1-3l 69% (>95:5)

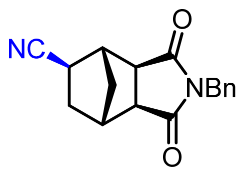
Activated



1-3m 65%

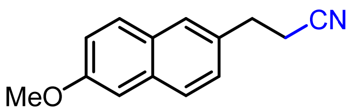


1-3n 85%

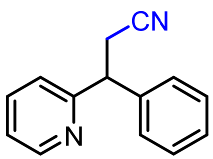


1-3o 92%

Drug Precursors

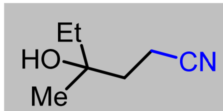


1-3p 96% (80:20)

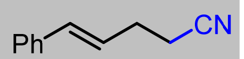


1-3q 47% (>95:5)

Unsuccessful Examples



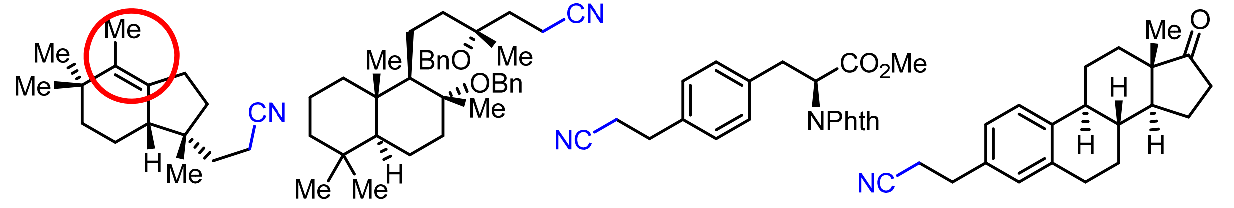
1-3r 0%



1-3s 0%

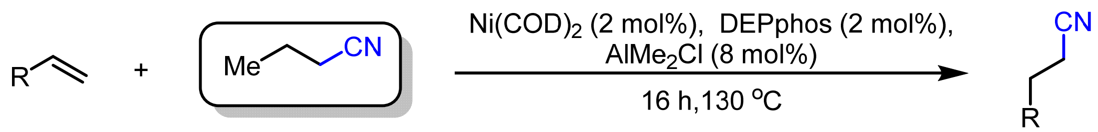
Exploration of hydrocyanation substrate scope

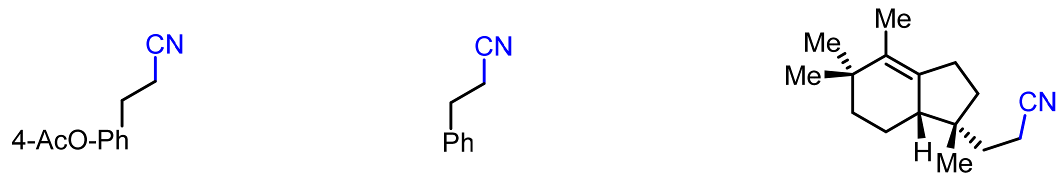
Late-stage Transfer Hydrocyanation



1-3t 95% (>95:5) **1-3u** 62% (>95:5) **1-3v** 88% (87:13) **1-3w** 81% (79:21)

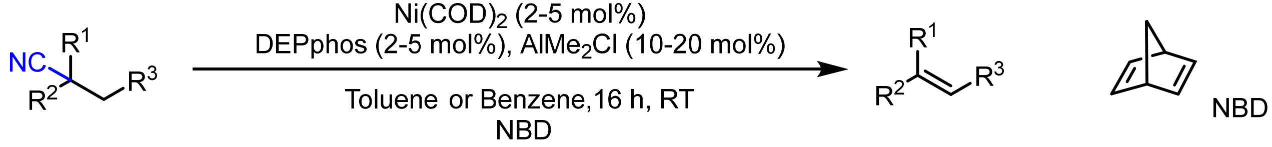
Scale-up Using an Inexpensive Reagent





1-3x **3.5 g**, 93% (85:15) **1-3e** **4.95 g**, 94% (82:18) **1-3t** **4.3 g**, 93% (>95:5)

Exploration of retro-hydrocyanation substrate scope

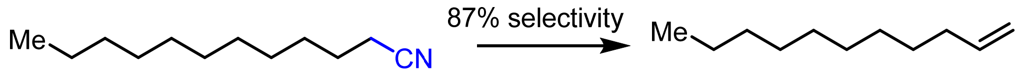


1-5 **1-6**

Styrene Synthesis

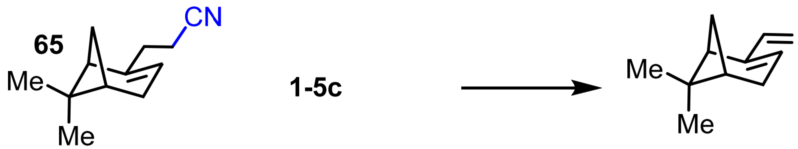
1-5a **1-6a** 94%

Aliphatics

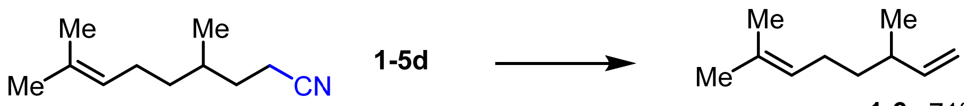


1-5b **1-6b** 93%

Terpene Derivatives



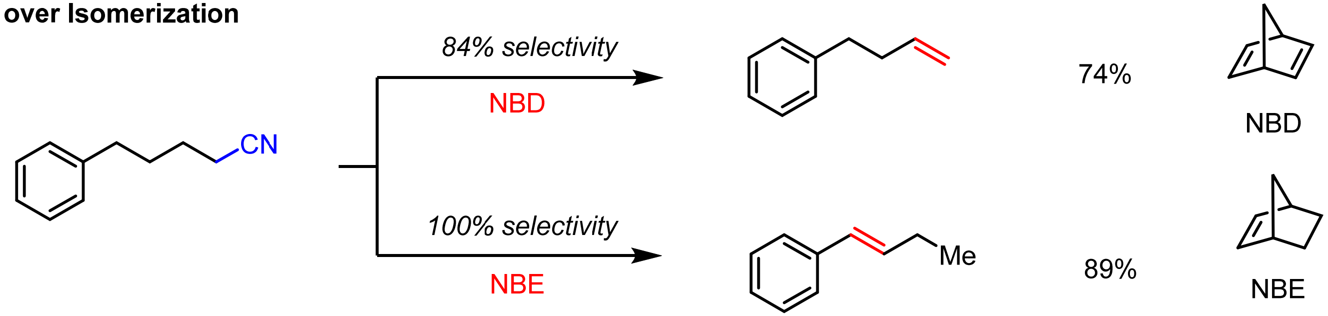
1-5c **1-6c** 73%



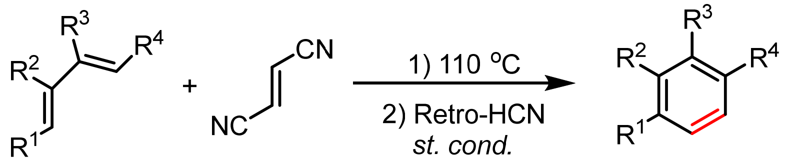
1-5d **1-6c** 71%

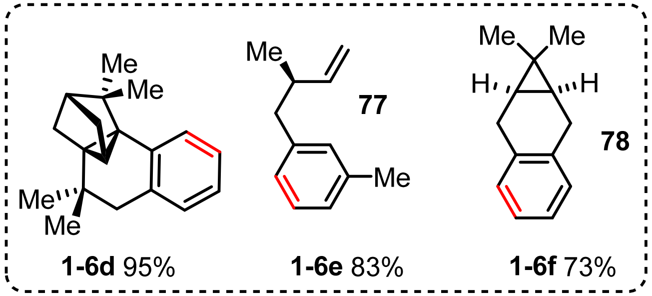
Exploration of retro-hydrocyanation substrate scope

Control over Isomerization

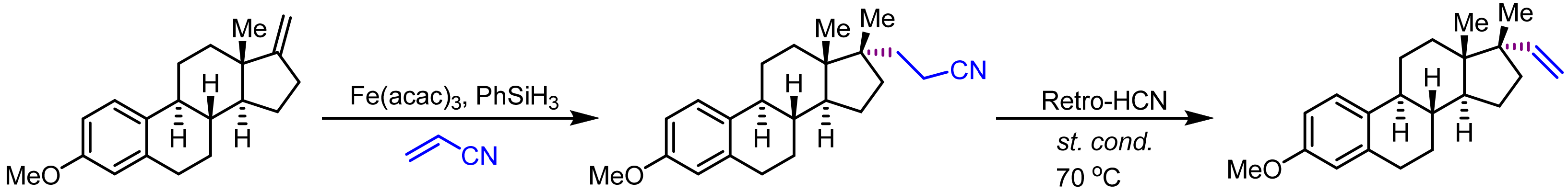


Construction of Aromatics from Dienes



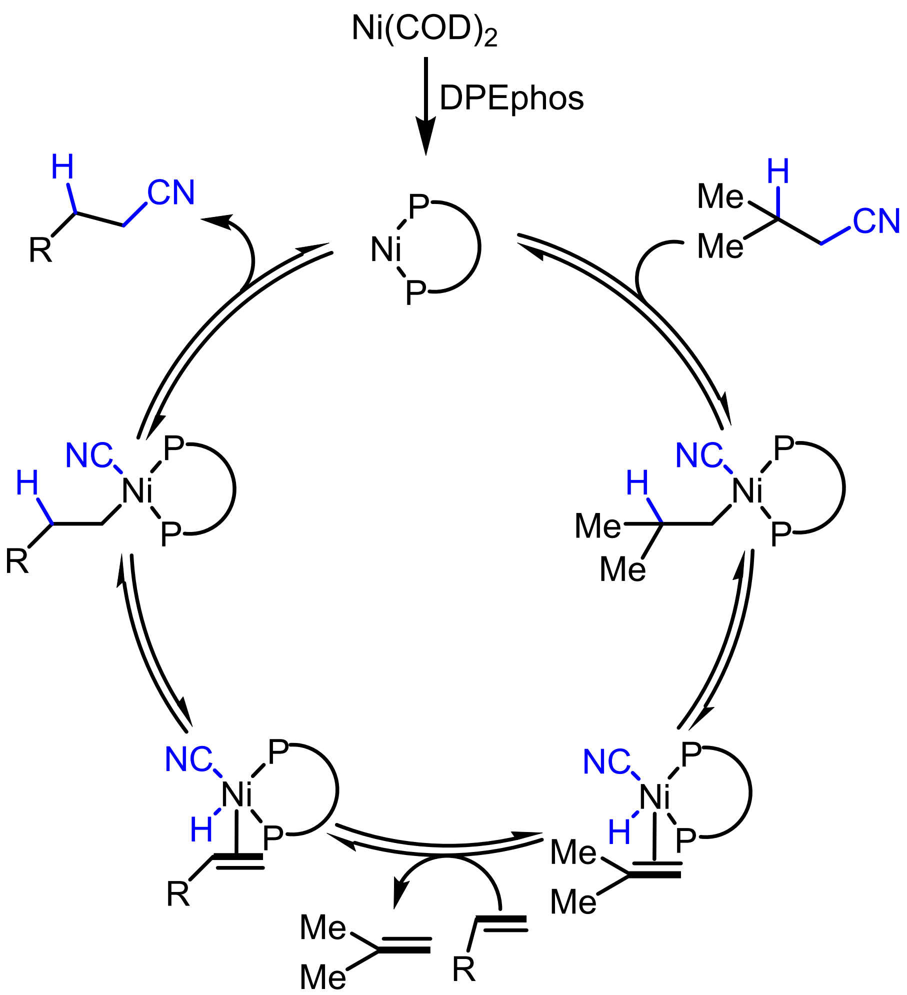


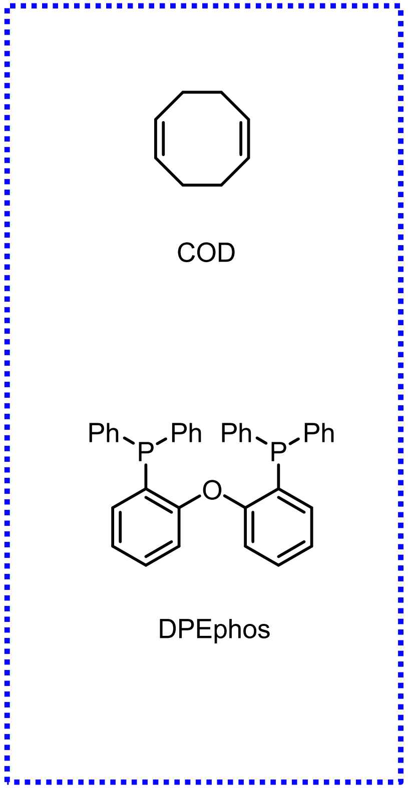
Stereoselective Installation of a Chiral Quaternary Vinyl Group



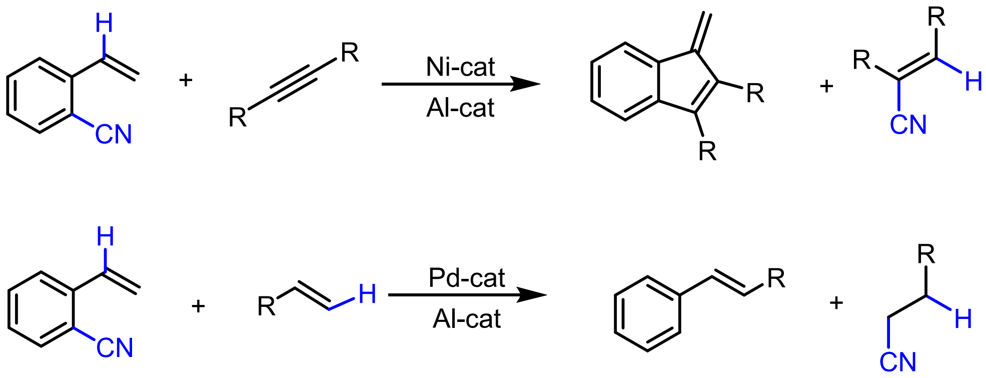
1-A **1-B** 80% (10:1 *dr*) **1-6g** 98% (10:1 *dr*)

Mechanism of the Transfer Hydrocyanation





Unlocking Mizoroki–Heck-type reactions of aryl cyanides using transfer hydrocyanation as a turnover-enabling step

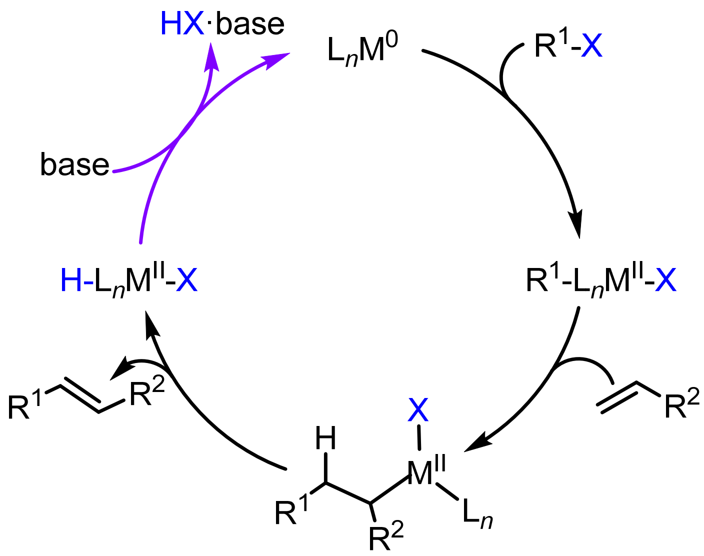


No HCN!
Irreversible!
Mizoroki–Heck-type!

Morandi, B. et al. *Chem. Eur. J.* **2016**, *22*, 15629.

Traditional Mizoroki–Heck reaction

Mechanism



$$H\text{-}L_nM^{II}\text{-}X + \text{base} \longrightarrow L_nM^0 + HX{\bullet}\text{base}$$

Heck, R. F. et al. *Org. React*. **1982**, *27*, 345.

New approach for Mizoroki–Heck

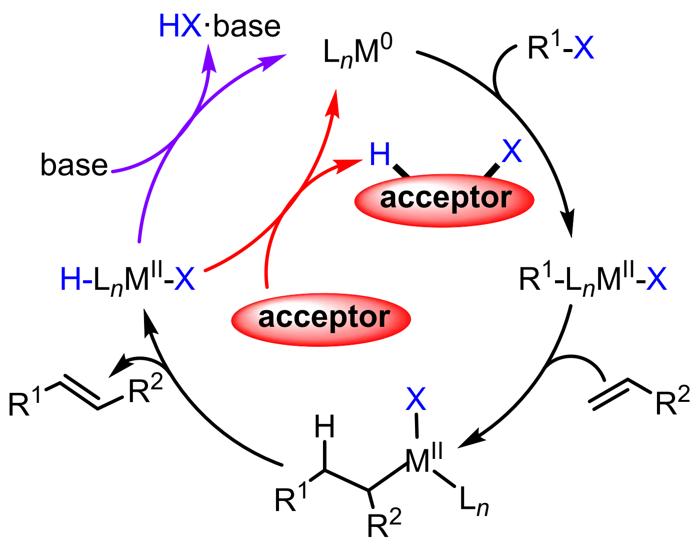
$$\text{Ar-CN} + L_nM^0 \xrightarrow{\text{Lewis acid}} \text{Ar-}L_nM^{II}\text{-CN}$$

Jacobsen, E. N. et al. *J. Am. Chem. Soc*. **2008**, *130*, 12594.

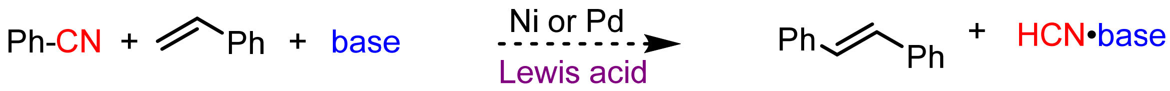
Shi, Z. J. et al. *Org. Lett*. **2009** ,*11*, 3374.

Jiao, N. et al. *Chem. Rev*. **2014**, *114*, 8613.

Mechanism

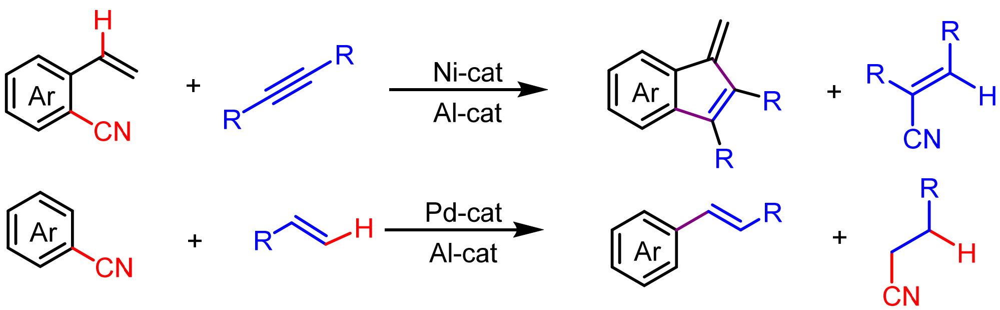


Transfer hydrocyanation for aryl cyanides

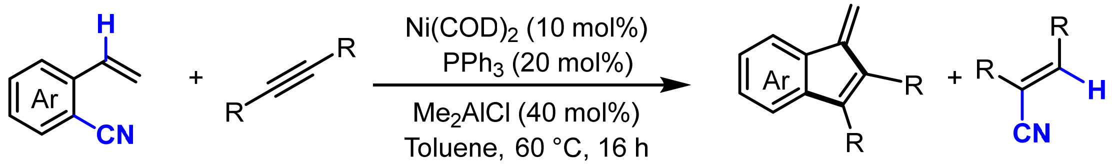


Results: ***no conversion*** using base only
low yield using base and Lewis acid

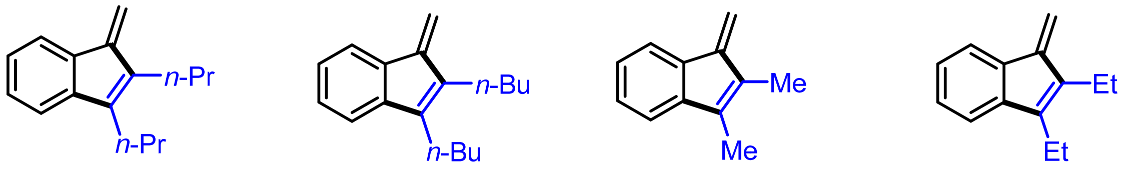
⇨ **needs** Lewis acid but only **low reactivity** in the presence of base



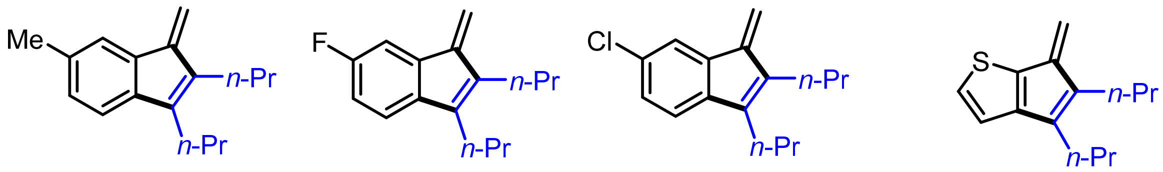
Scope of the intramolecular MH-type reaction



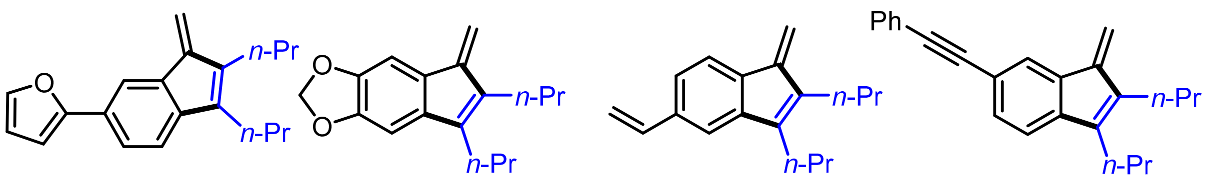
2-1 **2-2** **2-3** **2-4**



2-3a 81% yield
2-3b 89% yield
2-3c 67% yield
2-3d 73% yield

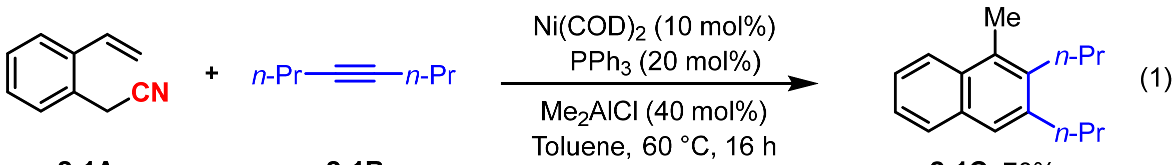


2-3e 80% yield
2-3f 70% yield
2-3g 89% yield
2-3h 66% yield

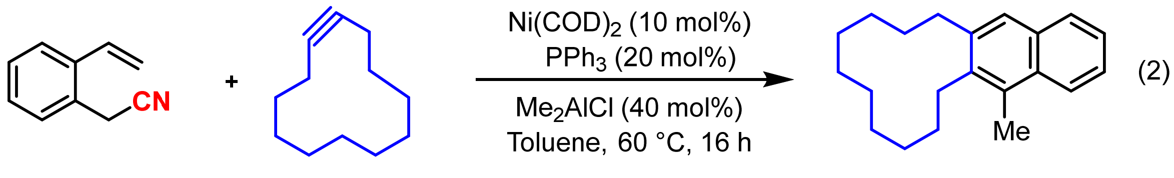


2-3i 45% yield
2-3j 70% yield
2-3k 76% yield
2-3l 58% yield

Synthesis of polysubstituted naphthalene compounds

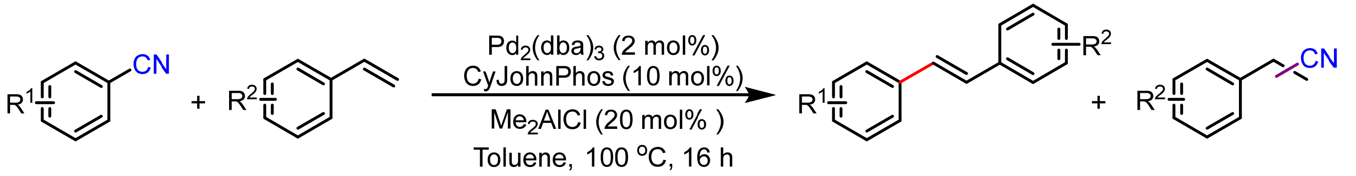


2-1A **2-1B** **2-1C**: 70%

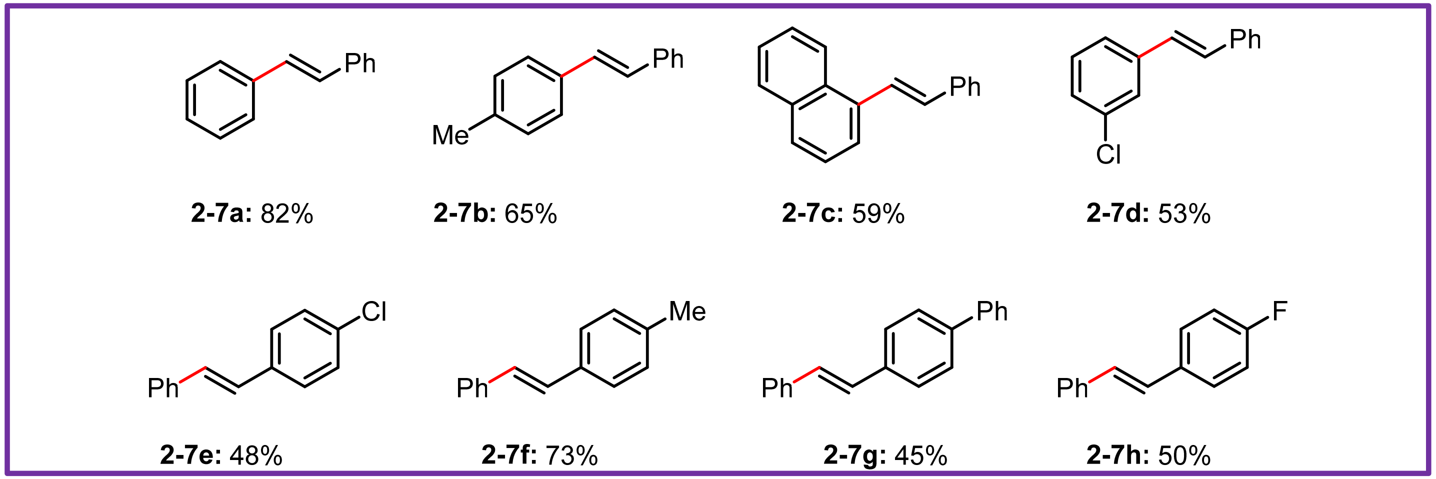


2-1A **2-1D** **2-1E**: 77%

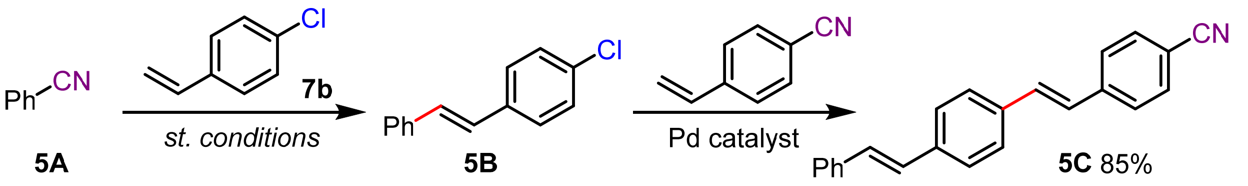
Scope of the intermolecular Heck-type reaction



2-5 **2-6** **2-7** **2-8**



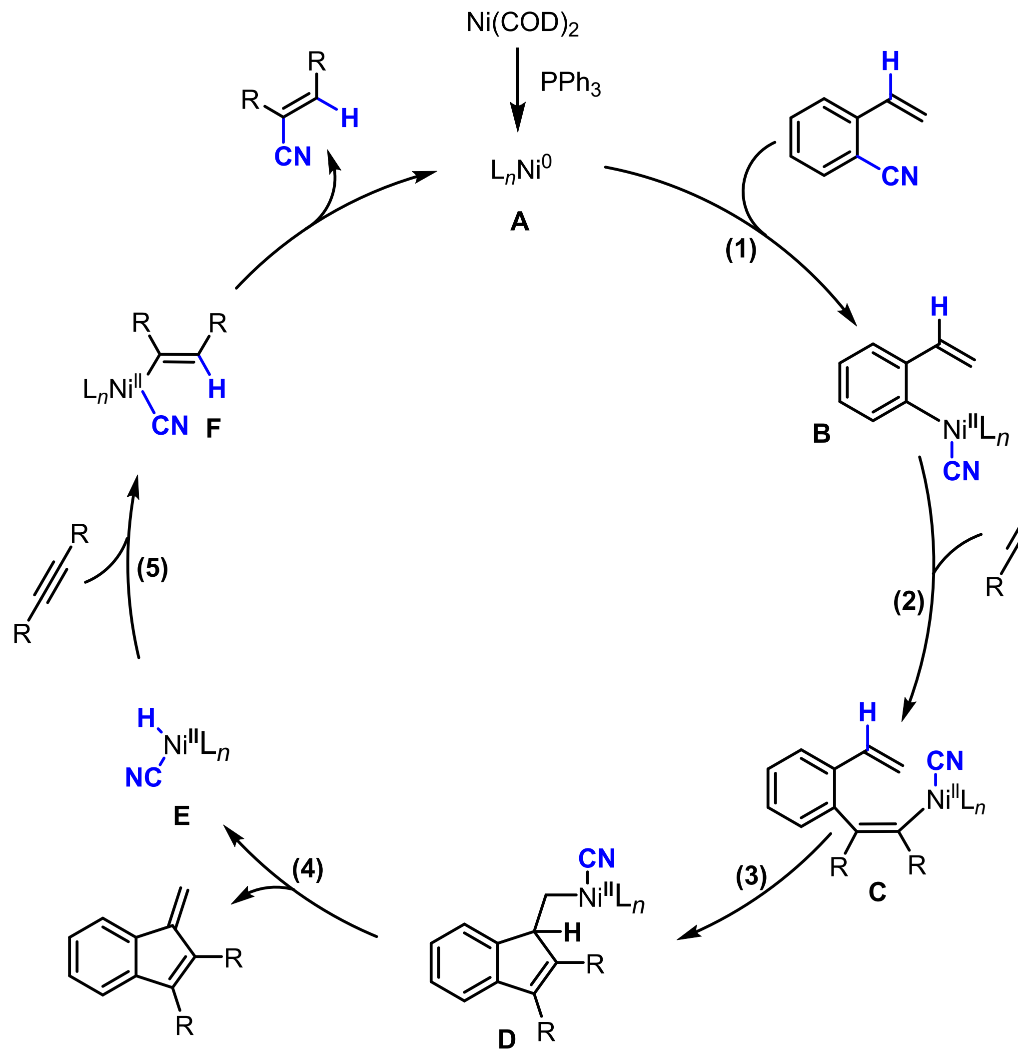
The application in the coupling reaction



CN cleavage in the presence of Cl

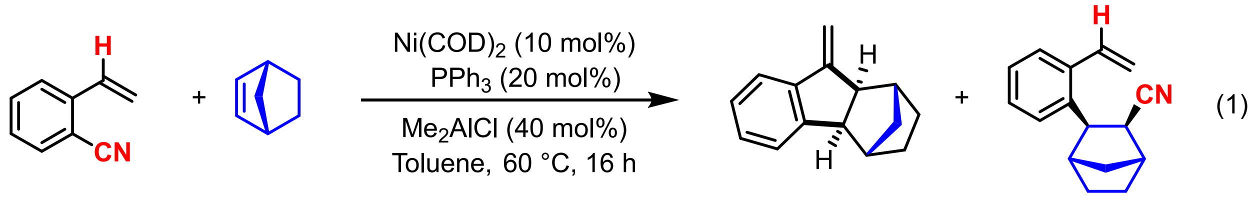
Cl cleavage in the presence of CN

Proposed mechanism

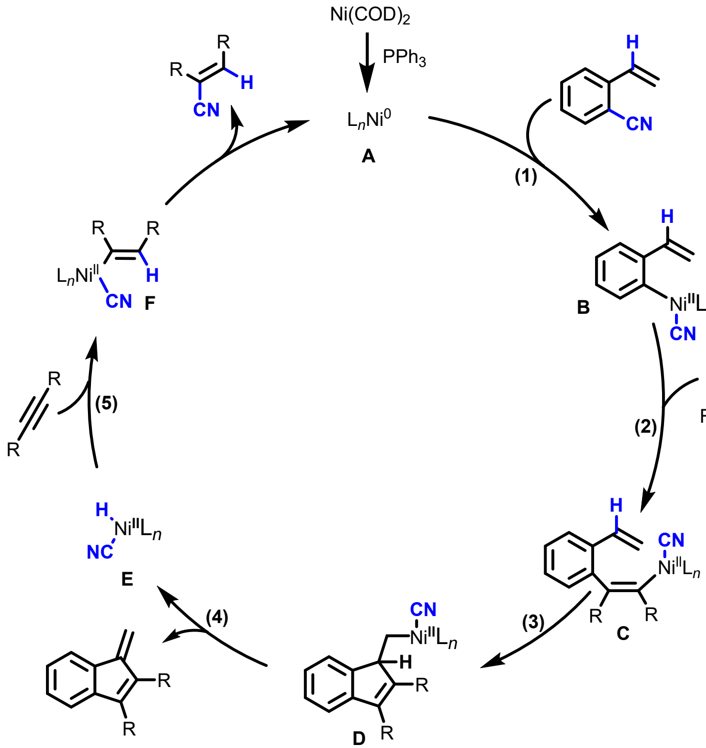


Mechanistic experiments

B → **C**

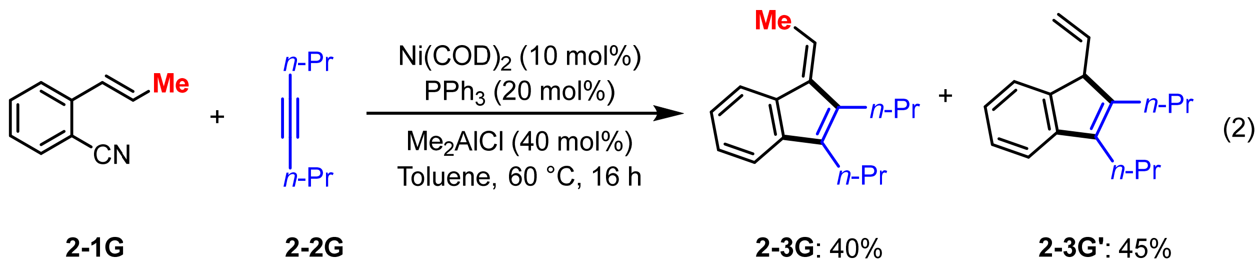


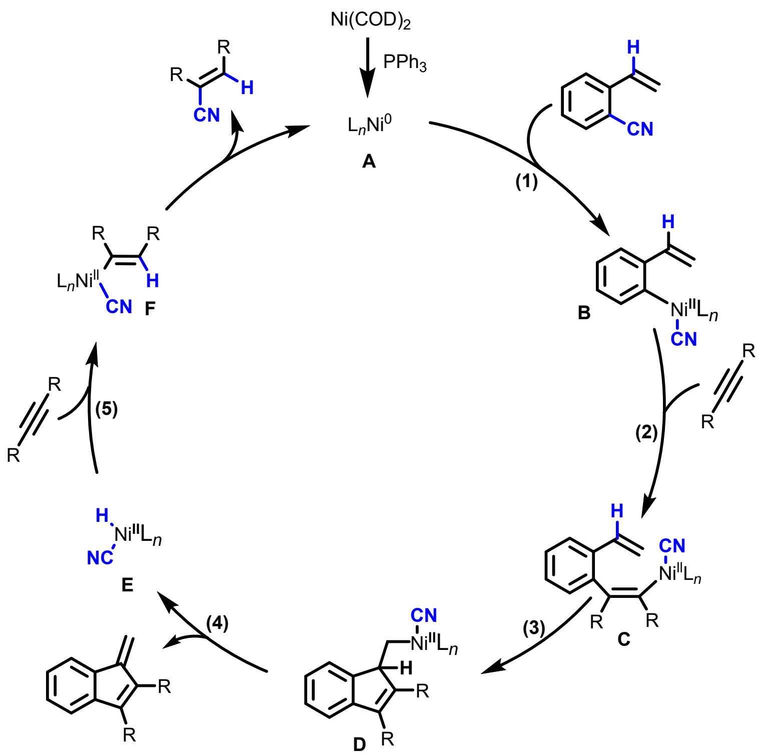
2-1F **2-2F** **2-3F**: 48% **2-4F**: 42%



Mechanistic experiments

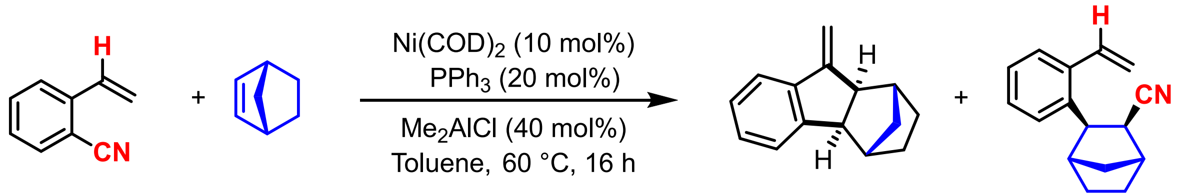
D → E





Mechanistic experiments

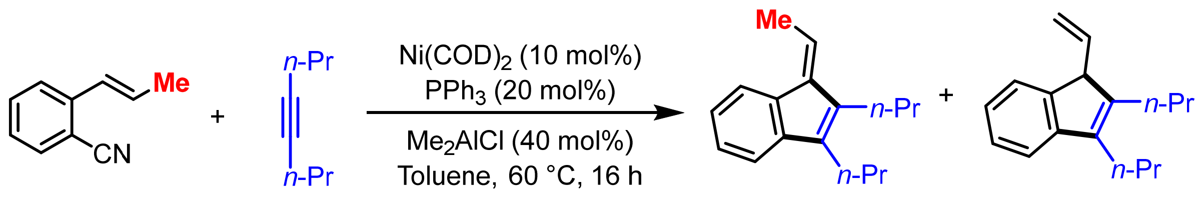
B → **C**



(1)

2-1F **2-2F** **2-3F**: 48% **2-4F**: 42%

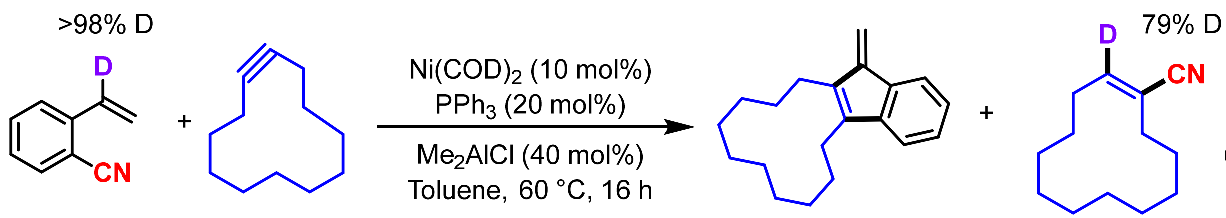
D → **E**



(2)

2-1G **2-2G** **2-3G**: 40% **2-3G'**: 45%

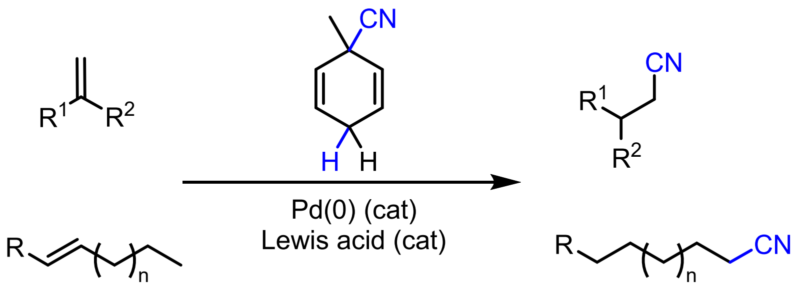
Deuterated experiment

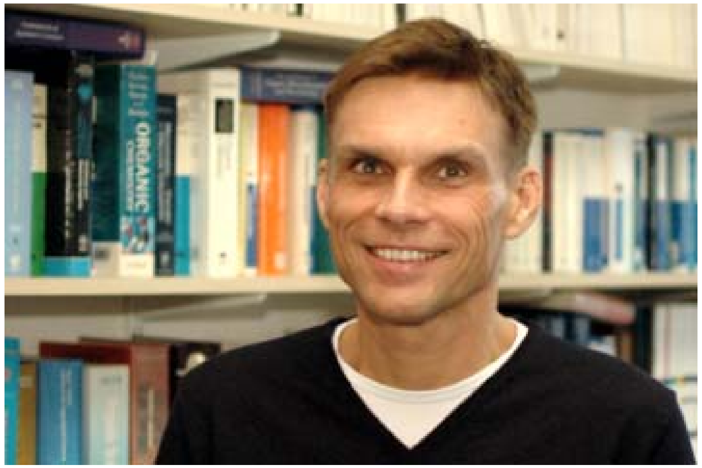


(3)

2-1H **2-2H** **2-3H**: 96% **2-4H**: 90%

Cooperative palladium/lewis acid-catalyzed transfer hydrocyanation of alkenes and alkynes

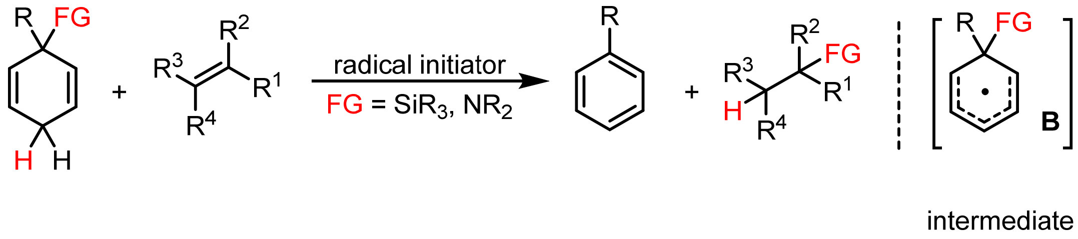




No HCN!
Anti-Markovnikov selectivity!
Broad scope!
Chain walking!

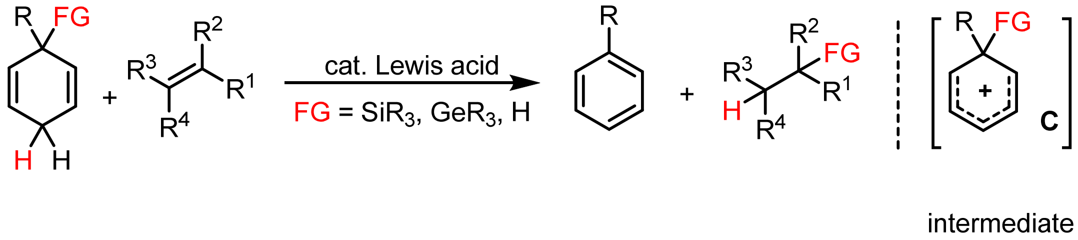
Studer, A. et al. *J. Am. Chem. Soc.* **2018**, *140*, 16353.

CHD core as reagents for functional group transfer reactions



Studer, A. et al. *Org. Lett*. **2001**, *3*, 2357.

Studer, A. et al. *Chem. Commun*. **2002**, 1592.



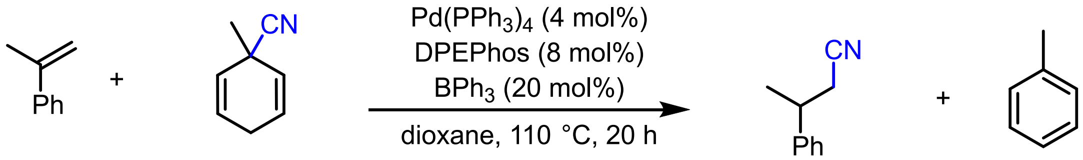
Oestreich, M. et al. *Angew. Chem. Int. Ed.* **2013**, *52*, 11905.

Oestreich, M. et al. *Org. Lett.* **2017**, *19*, 1898.

Oestreich, M. et al. *Angew . Chem. Int. Ed.* **2015**, *54*, 12158.

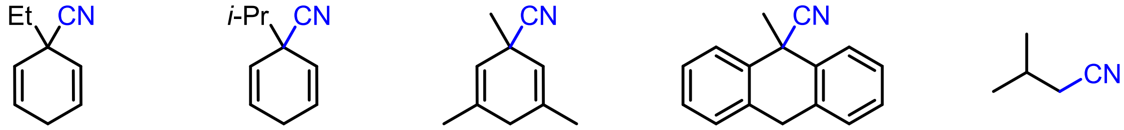
Oestreich, M. et al. *Angew. Chem. Int. Ed.* **2015**, *54*, 1965.

Palladium/lewis acid-cocatalyzed transfer hydrocyanation

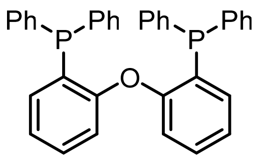


(1.0 equiv) (1.5 equiv)

3-1a **3-2a** **3-3a** 89%



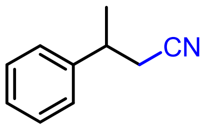
3-2b (53%) **3-2c** (39%) **3-2d** (22%) **3-2e** (0%) **3-2f** (15%)



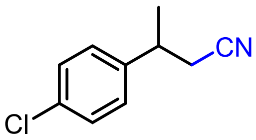
DPEphos

Transfer hydrocyanation of various alkenes and alkynes

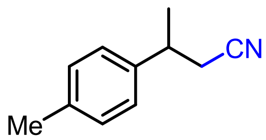
α-Substituted alkenes



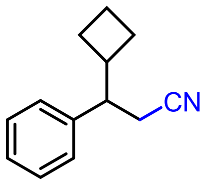
3-1b 89%



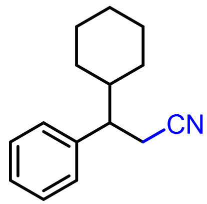
3-1c 80%



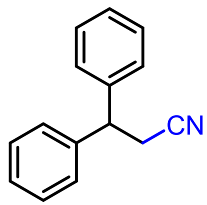
3-1d 86%



3-1e 87%

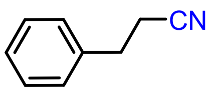


3-1f 78%

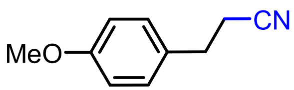


3-1g 59%

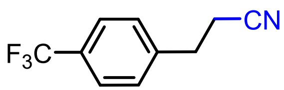
Styrenes



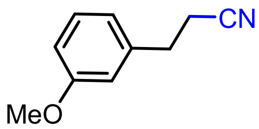
3-1h 90% (90:10)



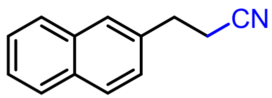
3-1i 87% (91:9)



3-1j 94% (90:10)

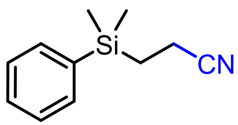


3-1k 82% (89:11)

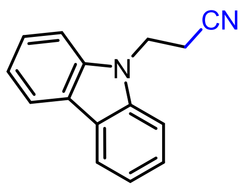


3-1l 95% (90:10)

Activated alkenes



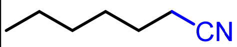
3-1m 96%



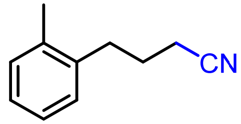
3-1n 83%

Transfer hydrocyanation of various alkenes and alkynes

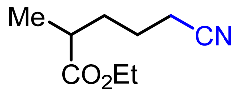
Aliphatic alkenes



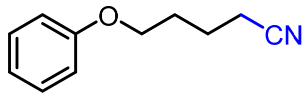
3-1o 99%



3-1p 81% (90:10)

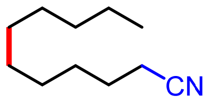


3-1q 78% (85:15)

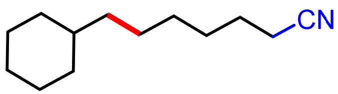


3-1r 85% (90:10)

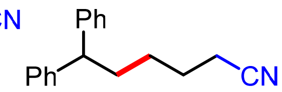
Chain walking hydrocyanation of internal alkenes



3-1s 75% (86:14)



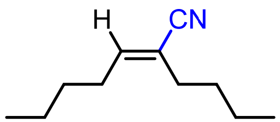
3-1t 73% (78:22)



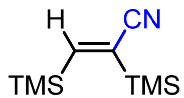
3-1u 77% (82:18)

3-1v 67% (84:16)

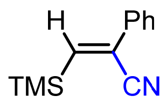
Alkynes



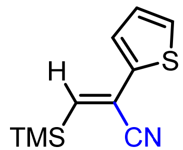
3-1w 87%



3-1x 33%



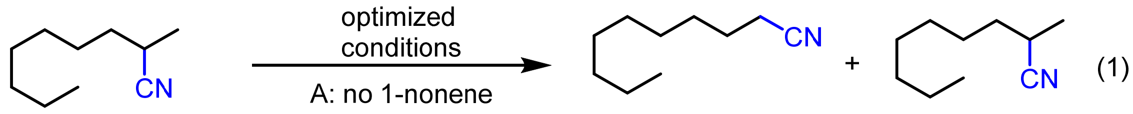
3-1y 62%



3-1z 72%

Mechanistic studies

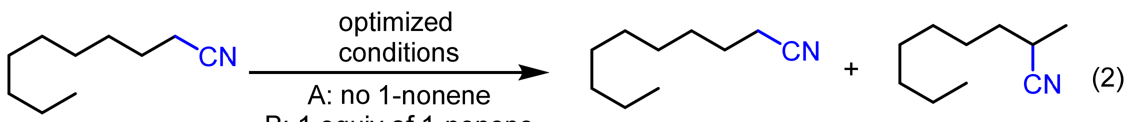
Isomerization research



3-1ax

3-1ax' (0%, A)
3-1ax' (10%, B)

3-1ax (99%, A)
3-1ax (90%, B)



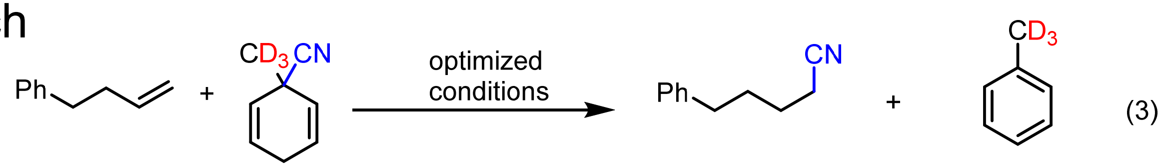
3-1ax'

3-1ax' (99%, A)
3-1ax' (99%, B)

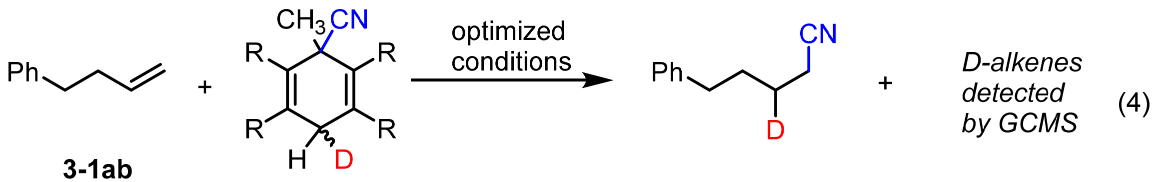
3-1ax (0%, A)
3-1ax (<1%, B)

These results show that the branched nitrile can be transferred to the linear nitrile

Deuterated research



3-1ab **3-2a-d3** **3-1ab-H** 76% (0% D) *detected by GCMS*



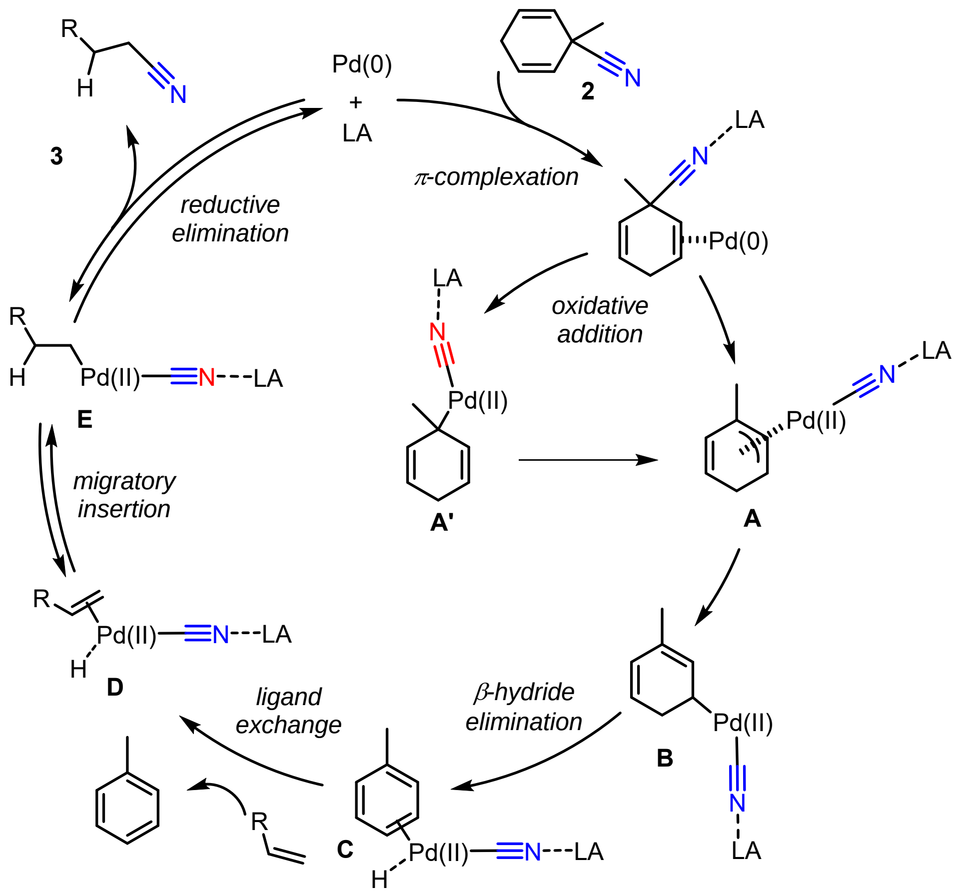
3-1ab

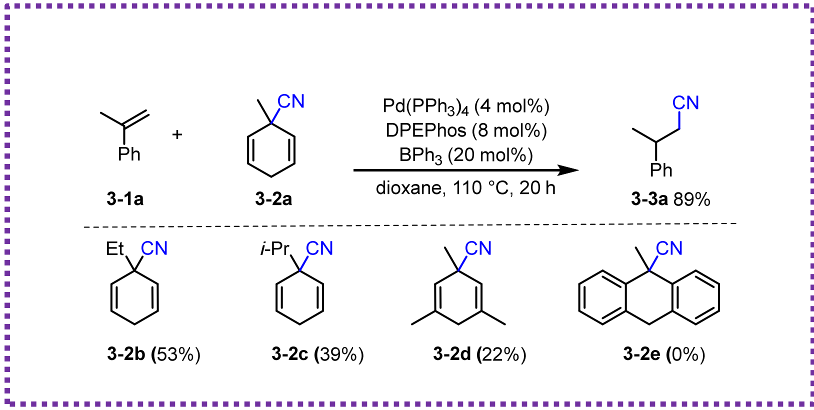
R = H, **3-2a-d1** (*dr* = 1:1)
R = D, **3-2a-d5** (*dr* = 1:1)

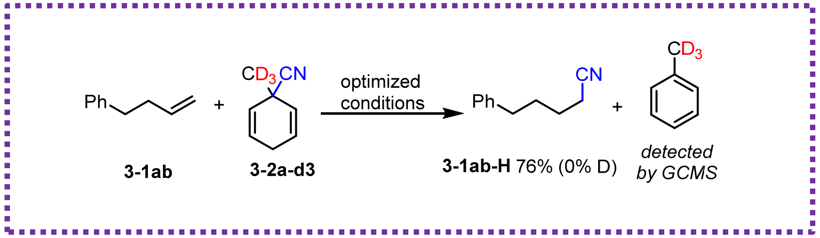
3-1ab-D 71% (20% D)
3-1ab-D 69% (20% D)

These results show that the H atom is derived from the methylene group

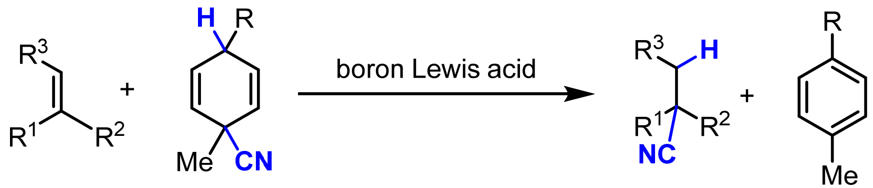
Proposed mechanism







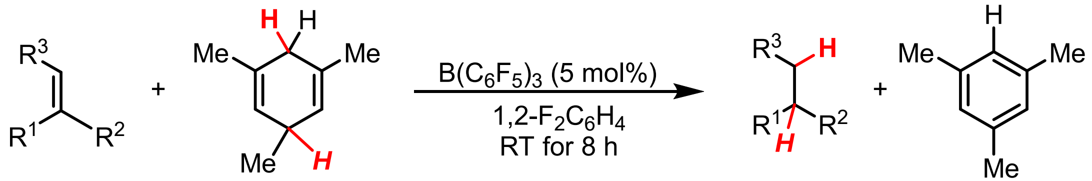
Transfer hydrocyanation of α- and α,β -substituted styrenes catalyzed by boron lewis acids



No HCN!
Markovnikov selectivity!

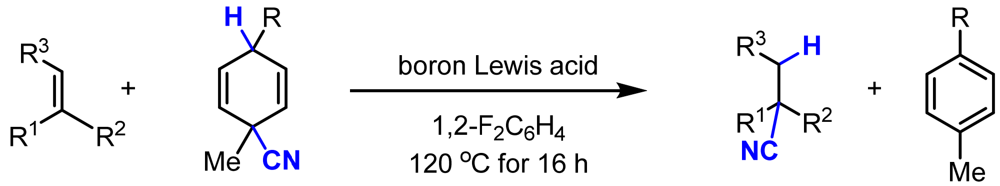
Oestreich, M. et al. *Angew. Chem. Int. Ed.* **2019**, *58*, 3579.

CHD core as reagents for functional group transfer reactions



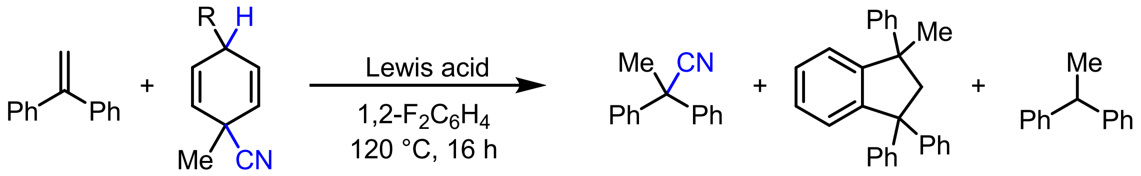
Oestreich, M. et al. *Chem. Sci*. **2017**, *8*, 4688.

Oestreich, M. et al. *Org. Lett*. **2016**, *18*, 2463.



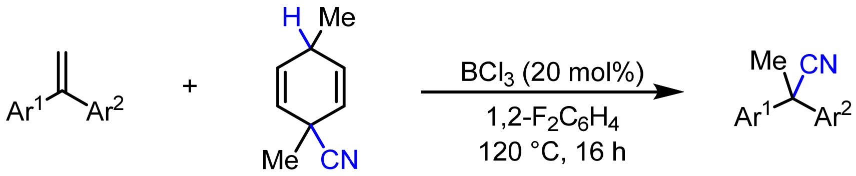
R = H or Me

Transfer hydrocyanation catalyzed by boron lewis acids

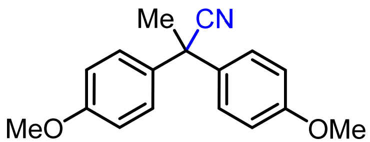


Entry	Lewis acid (mol%)	Surrogate	**4-4a/4-5a/4-6a**	Conv. [%]
1	$B(C_6F_5)_3$ (20)	4-1	42:14:44	> 99
2	$B(C_6F_5)_3$ (100)	4-1	20:70:10	> 99
3	$B(C_6F_5)_3$ (100)	4-2	18:79:3	> 99
4	BCl_3 (20)	4-2	99:1:0	> 99
5	BCl_3 (20)	4-1	94:3:3	> 99
6	BCl_3 (10)	4-2	93:7:0	> 99
7	BBr_3 (20)	4-2	88:11:1	> 99
8	$BF_3{\cdot}OEt_2$ (20)	4-2	38:62:0	85
9	$B(OMe)_3$ (20)	4-2	-	0
10	$AlCl_3$ (20)	4-1	40:49:11	> 99
11	$AlCl_3$ (20)	4-2	47:52:1	99

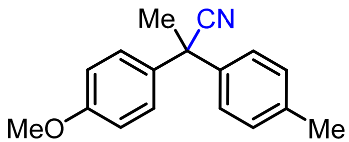
Transfer hydrocyanation of various 1,1-diarylethylenes with BCl_3



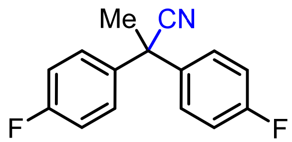
4-3 **4-2** **4-4**



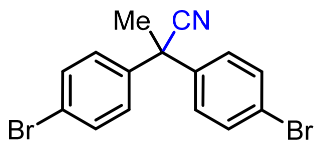
4-4b: 99%



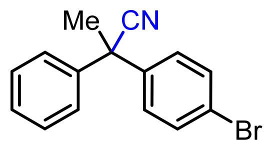
4-4c: 83%



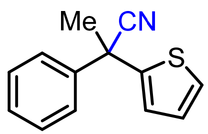
4-4d: 94%



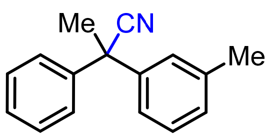
4-4e: 48%



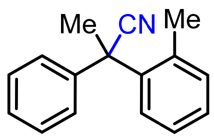
4-4f: 60%



4-4g: 65%

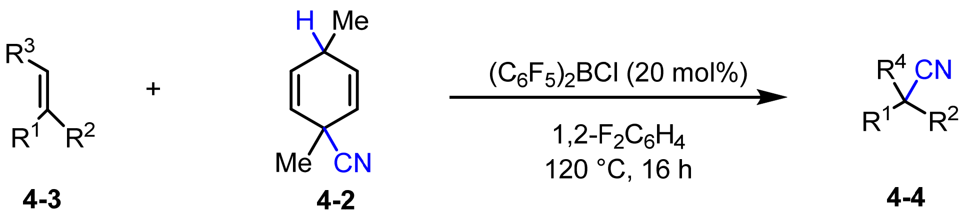


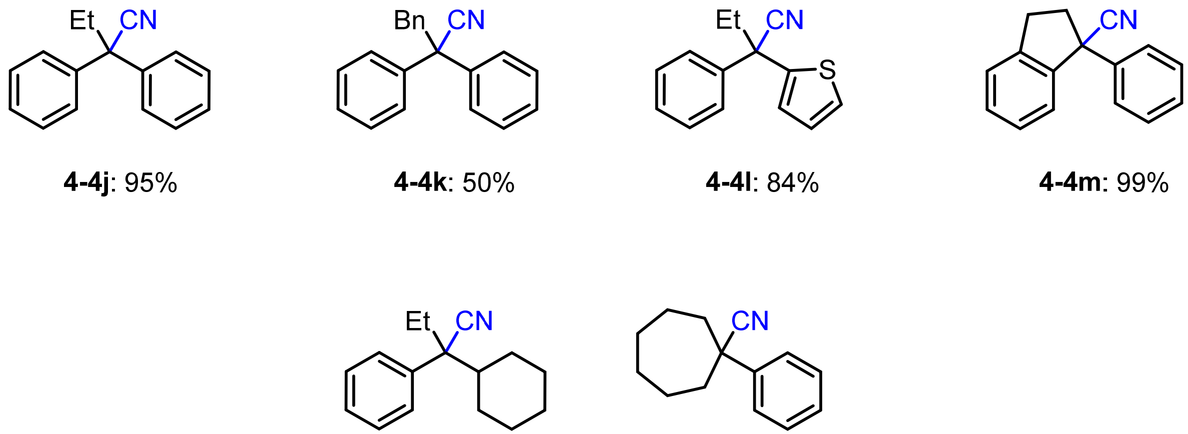
4-4h: 50%



4-4i: 45%

Transfer hydrocyanation of trisubstituted alkenes with $(C_6F_5)_2BCl$





4-4j: 95%

4-4k: 50%

4-4l: 84%

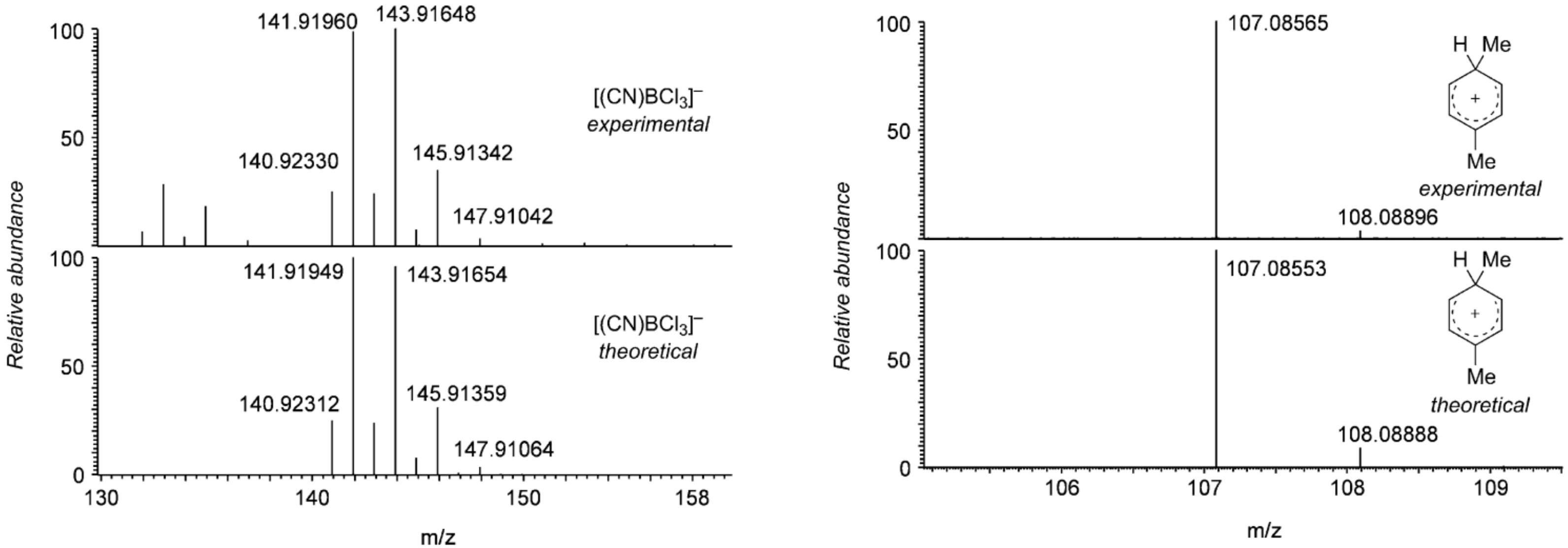
4-4m: 99%

4-4n: 88%

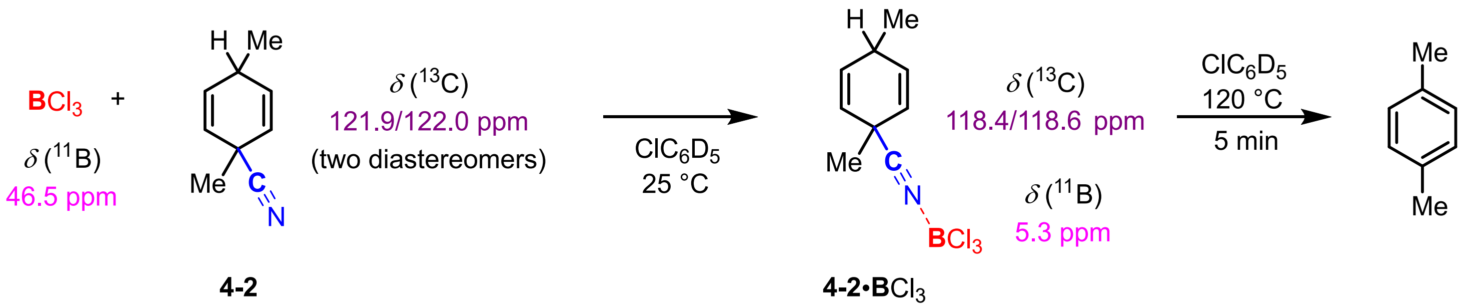
4-4o: 50%

Mechanism studies

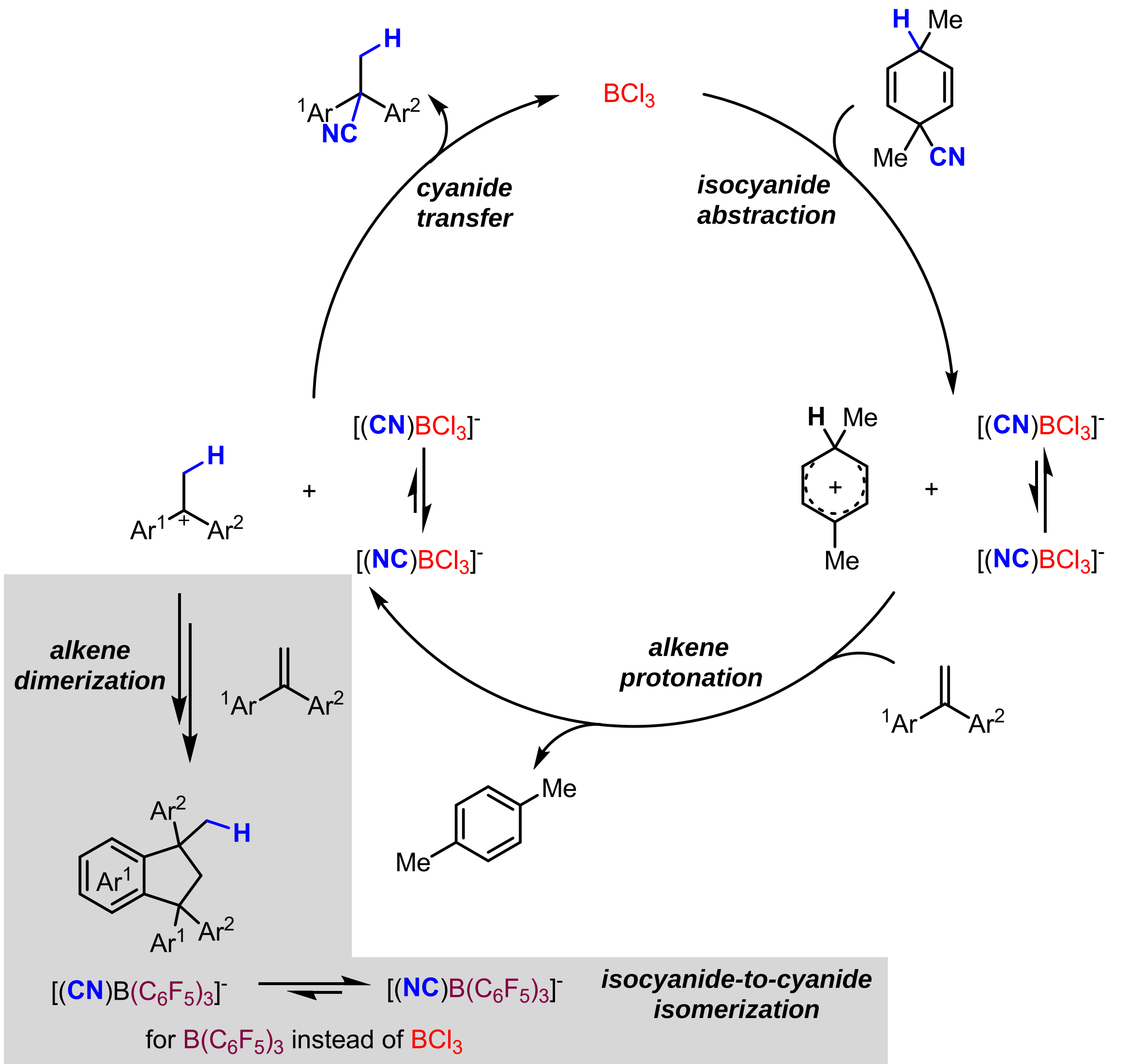
In-situ ESI-MS spectra



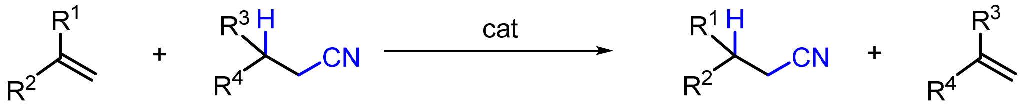
Stoichiometric NMR experiment



Proposed mechanism



Summary



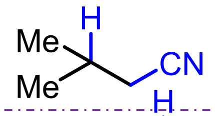
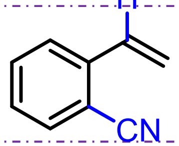
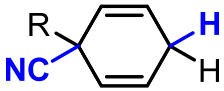
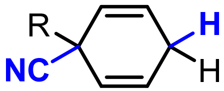
No HCN !

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

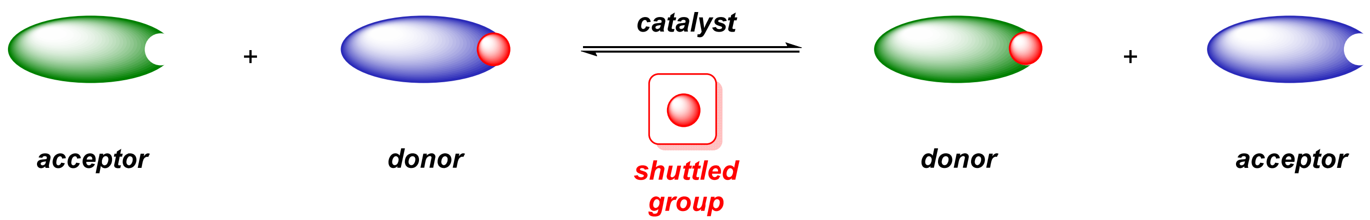
2 Morandi, B. et al. *Chem. Eur. J.* **2016**, *22*, 15629.

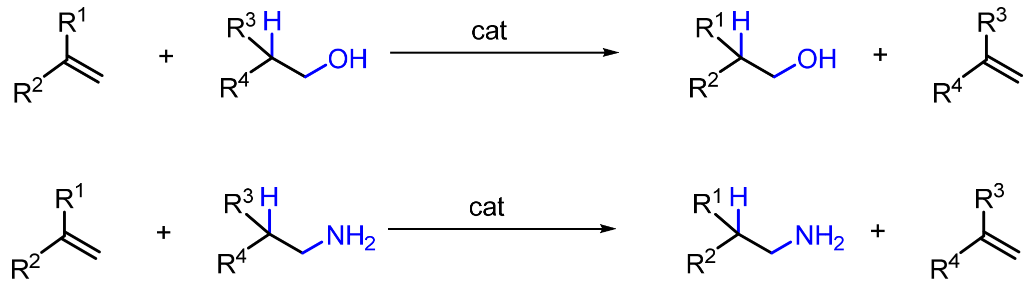
3 Studer, A. et al. *J. Am. Chem. Soc.* **2018**, *140*, 16353.

4 Oestreich, M. et al. *Angew. Chem. Int. Ed.* **2019**, *58*, 3579

Entry	Cat	Surrogate	Driving forces	Selectivity
1	Ni/Al		gas release	Anti-Markovnikov
2	Ni/Al or Pd/LA		conjugated system	
3	Pd/LA		aromatization	Anti-Markovnikov
4	LA		aromatization	Markovnikov

Prospect


catalyst
acceptor
donor
shuttled group
donor
acceptor


R1
R2
R3 H
R4
OH
cat
R1 H
R2
OH
R3
R4
R1
R2
R3 H
R4
NH2
cat
R1 H
R2
NH2
R3
R4

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I am very grateful to everyone for listening, and I sincerely look forward to your comments and suggestions!