Literature Report 6

Regio- and Enantioselective Allylic Cyanomethylation by Synergistic Rhodium and Silane Catalysis

Reporter: Tong Niu

Checker: Bao-Qian Zhao

Sun, M.; Wei, L.; Li, C. *J. Am. Chem. Soc.* 2023, *145*, 3897

2023.05.22

CV of Prof. Changkun Li (李长坤)

Research:

Organometallic Chemistry & Asymmetric Catalysis & Organic Synthesis

Education & Professional Experience:

- **2000-2004** B.S., Chemistry, Peking University
- **2004-2010** Ph.D., Chemistry, Peking University
- **2010-2012** Postdoc., Kyoto University
  (Research mentor: Prof. Masahiro Murakami)
- **2012-2016** Postdoc., University of Freiburg
  (Research mentor: Prof. Bernhard Breit)
- **2016-2022** Tenure Track Associate Professor, SJTU
- **2022-Present** Associate Professor with Tenure, SJTU

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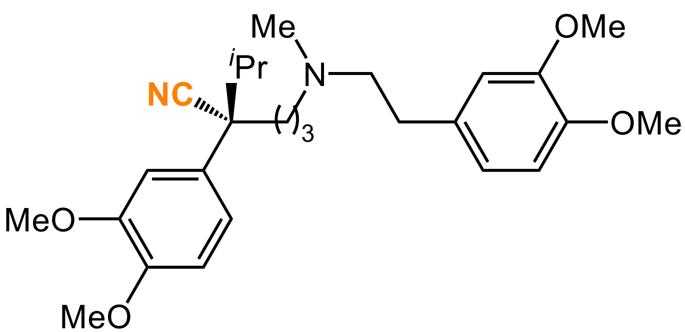
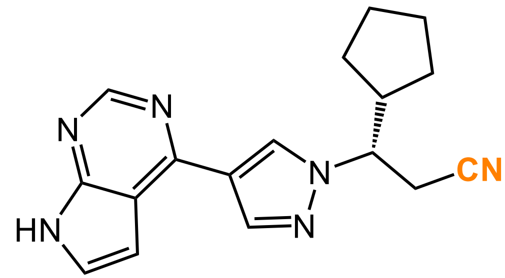
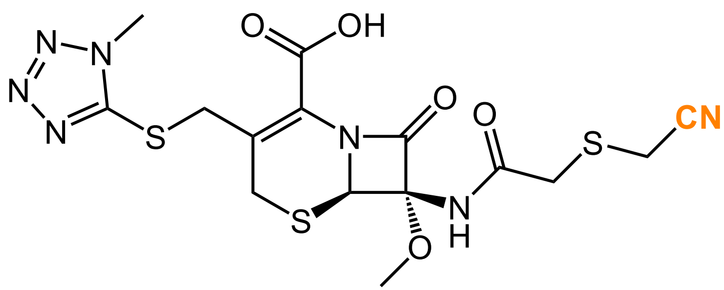
Nitrile-Containing Pharmaceuticals



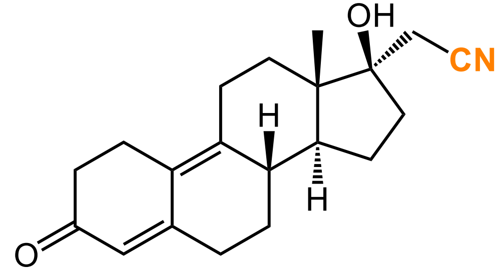
(*S*)-Verapamil



Ruxolitinib



Cefmetazole



Dienogest

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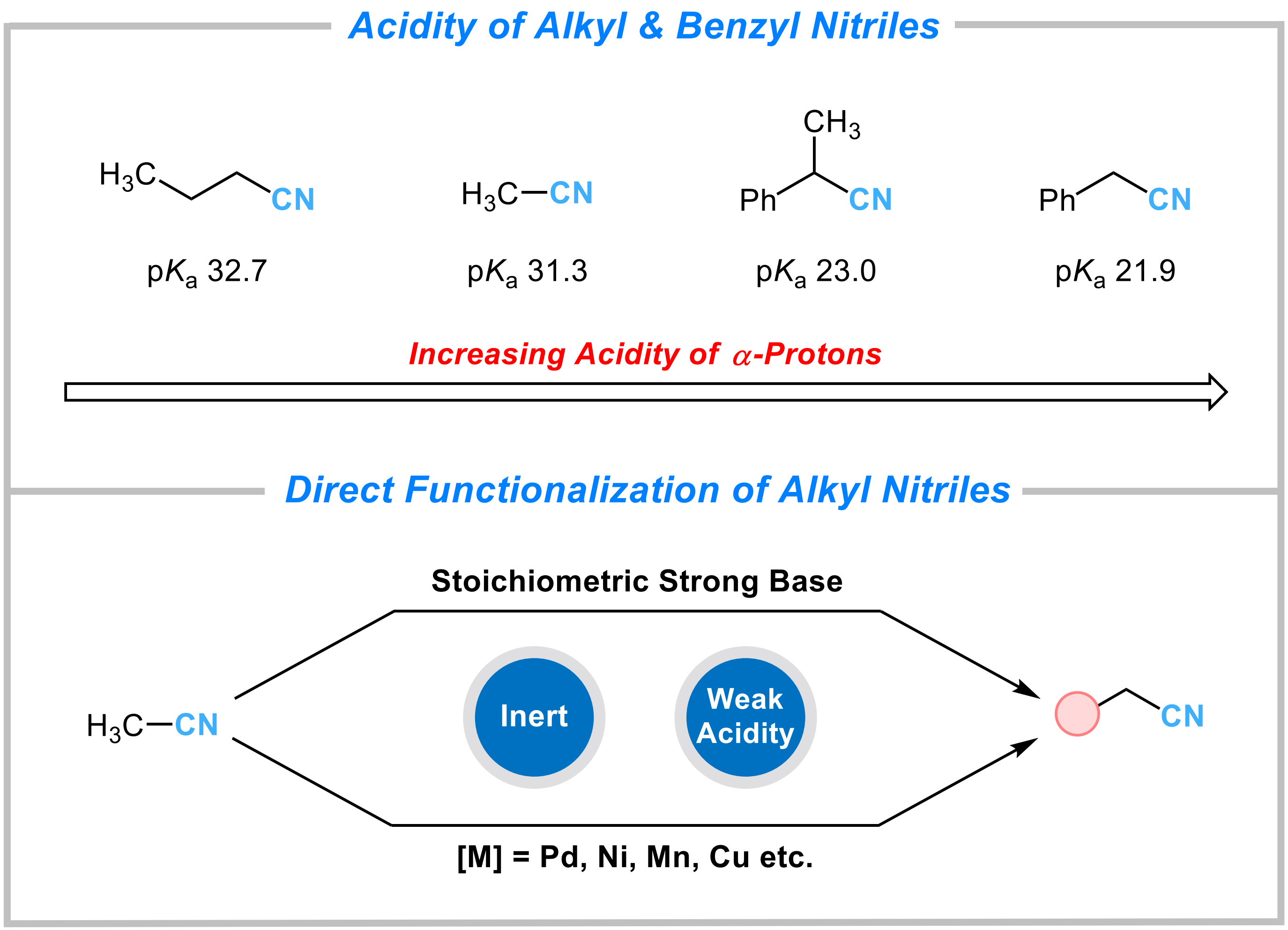
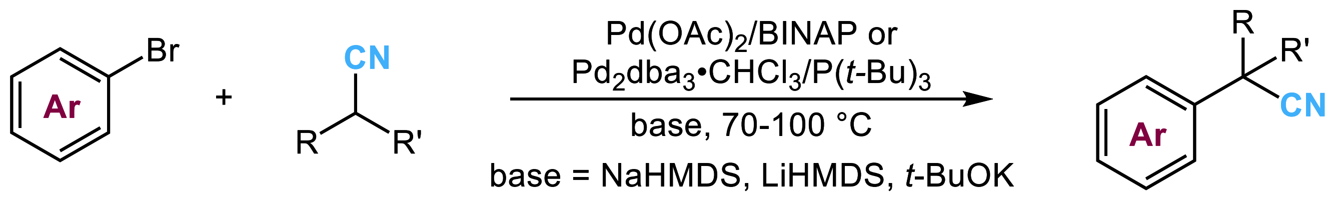
Introduction



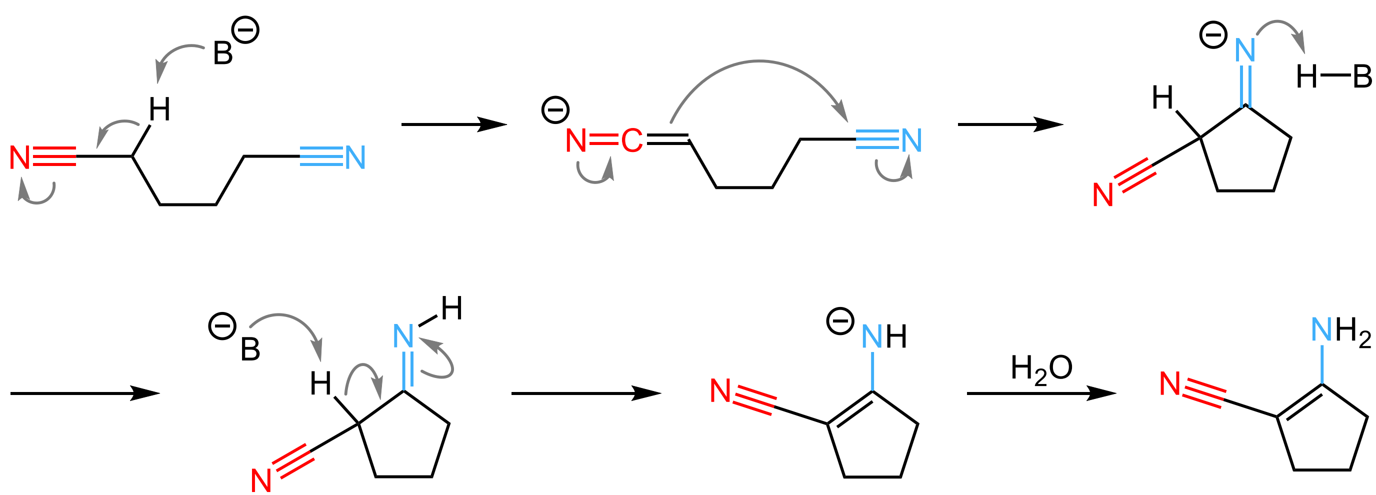
Tom, M.-J.; Evans, P. A. *J. Am. Chem. Soc.* **2020**, *142*, 11957

Direct Functionalization of Alkyl Nitriles

In the Presence of Stoichiometric Strong Base



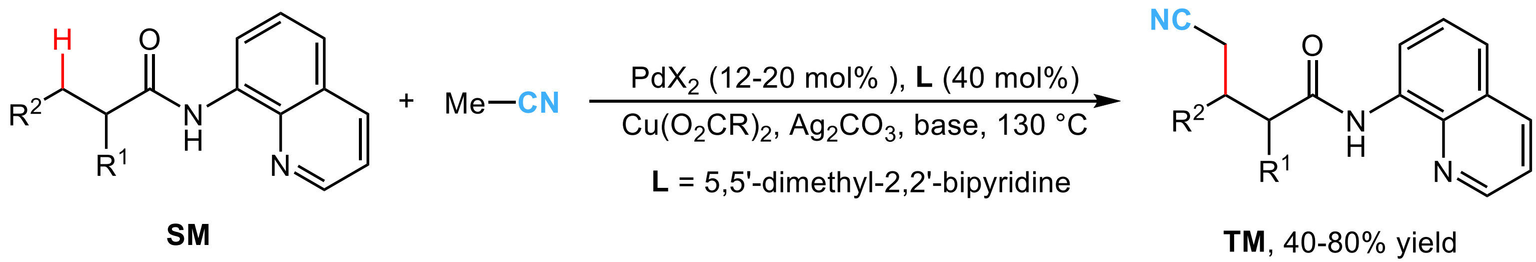
Thorpe Condensation

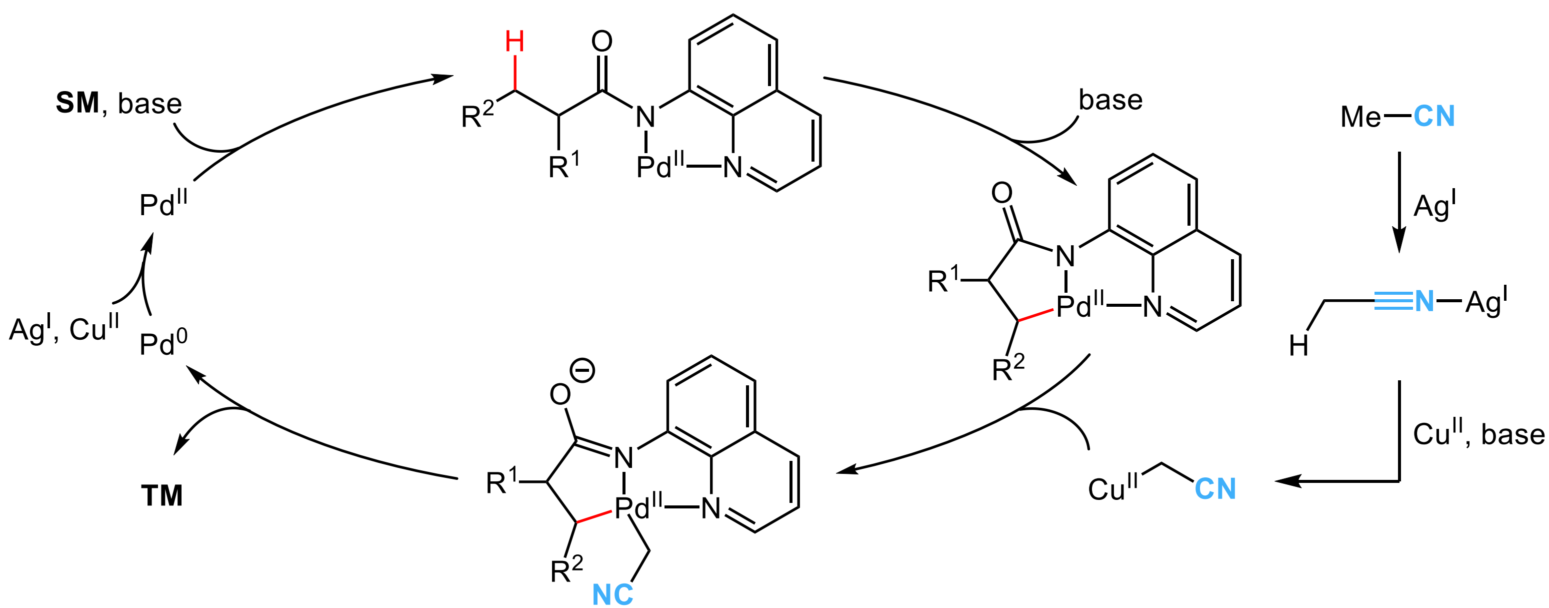


Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9330

Direct Functionalization of Alkyl Nitriles

Pd-Catalyzed Cyanomethylation of C(sp^3)-H with MeCN





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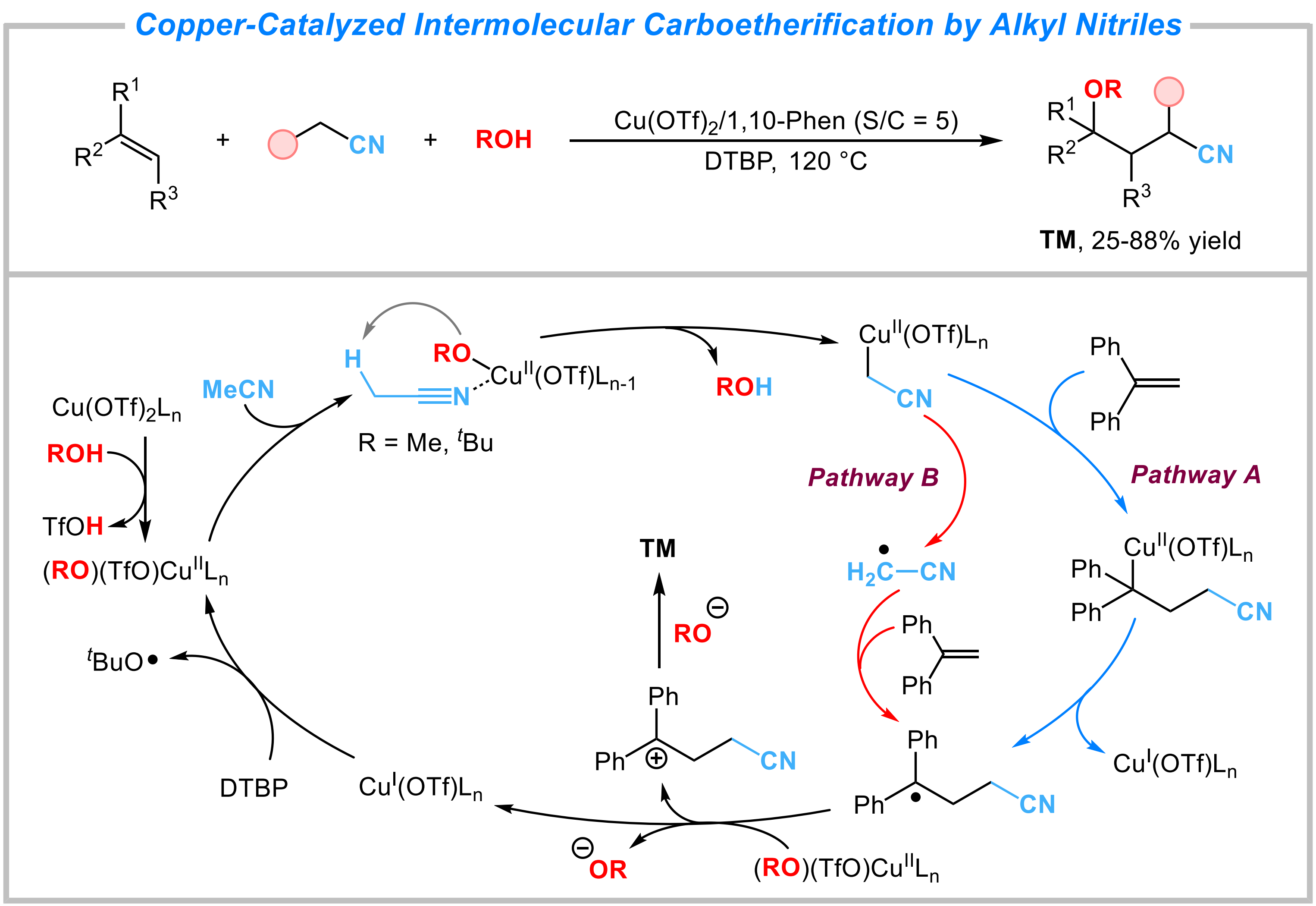
Direct Functionalization of Alkyl Nitriles



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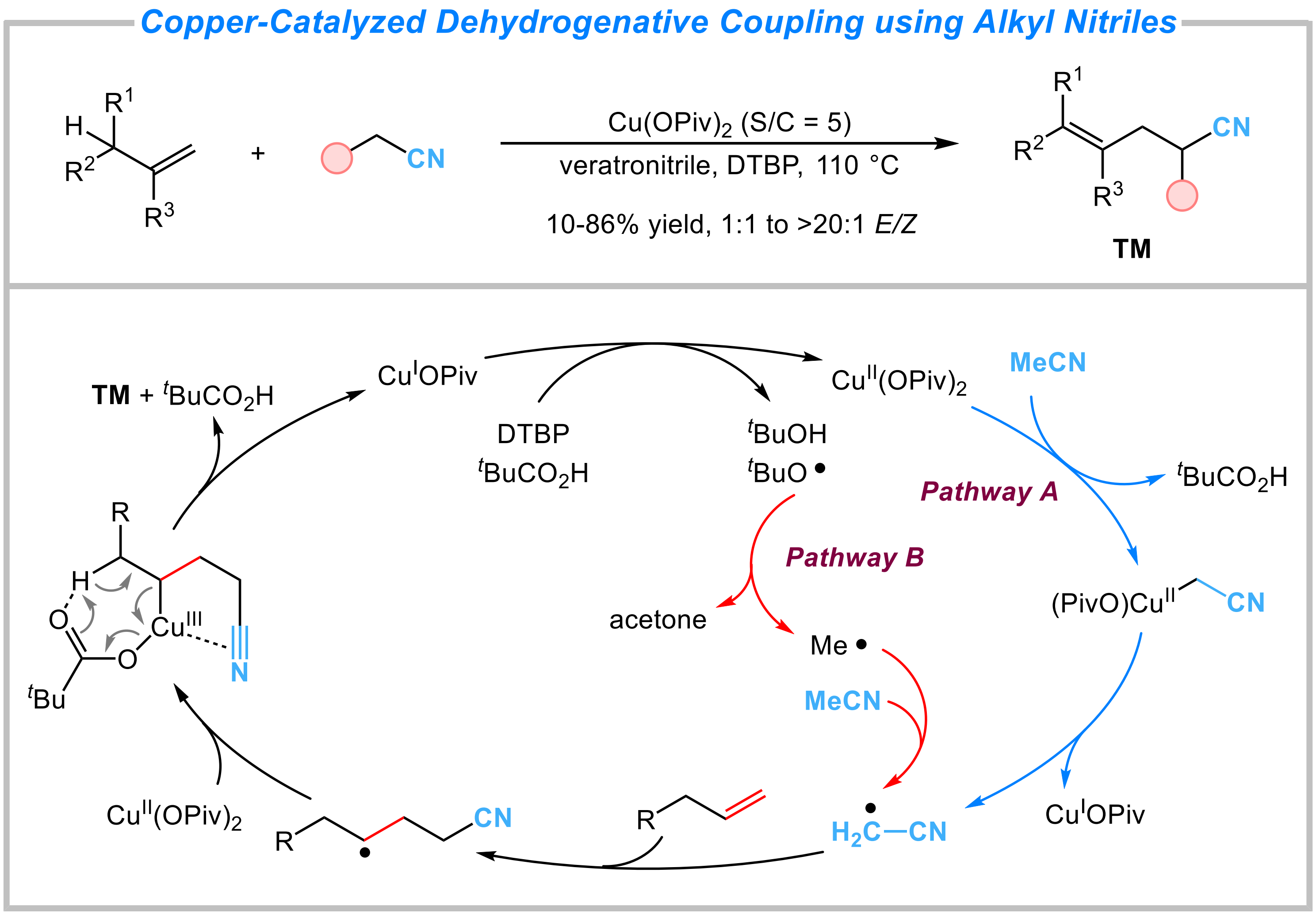
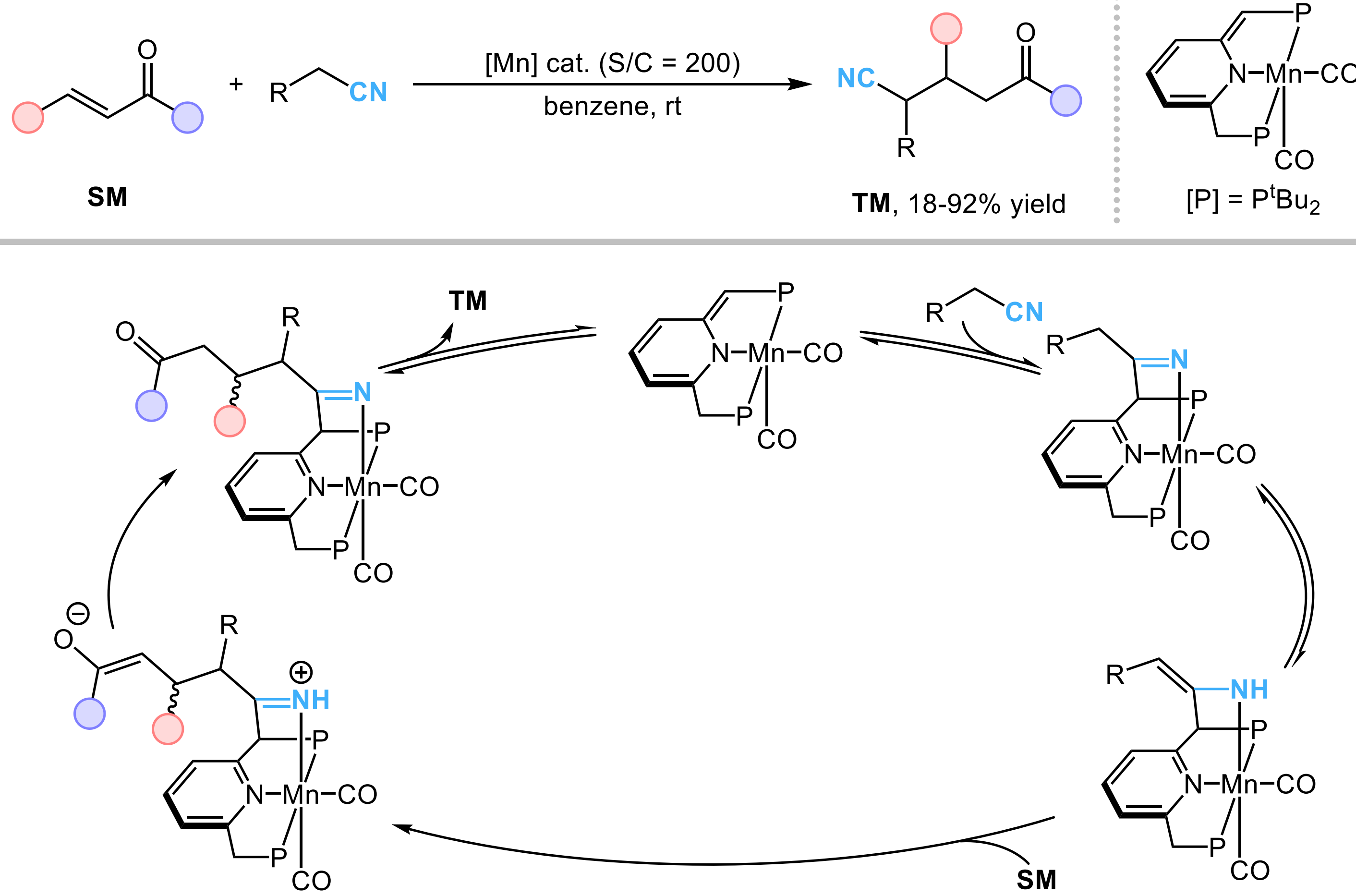
Direct Functionalization of Alkyl Nitriles



Wu, X.; Riedel, J.; Dong, V. M. *Angew. Chem. Int. Ed.* **2017**, *56*, 11589

Direct Functionalization of Alkyl Nitriles

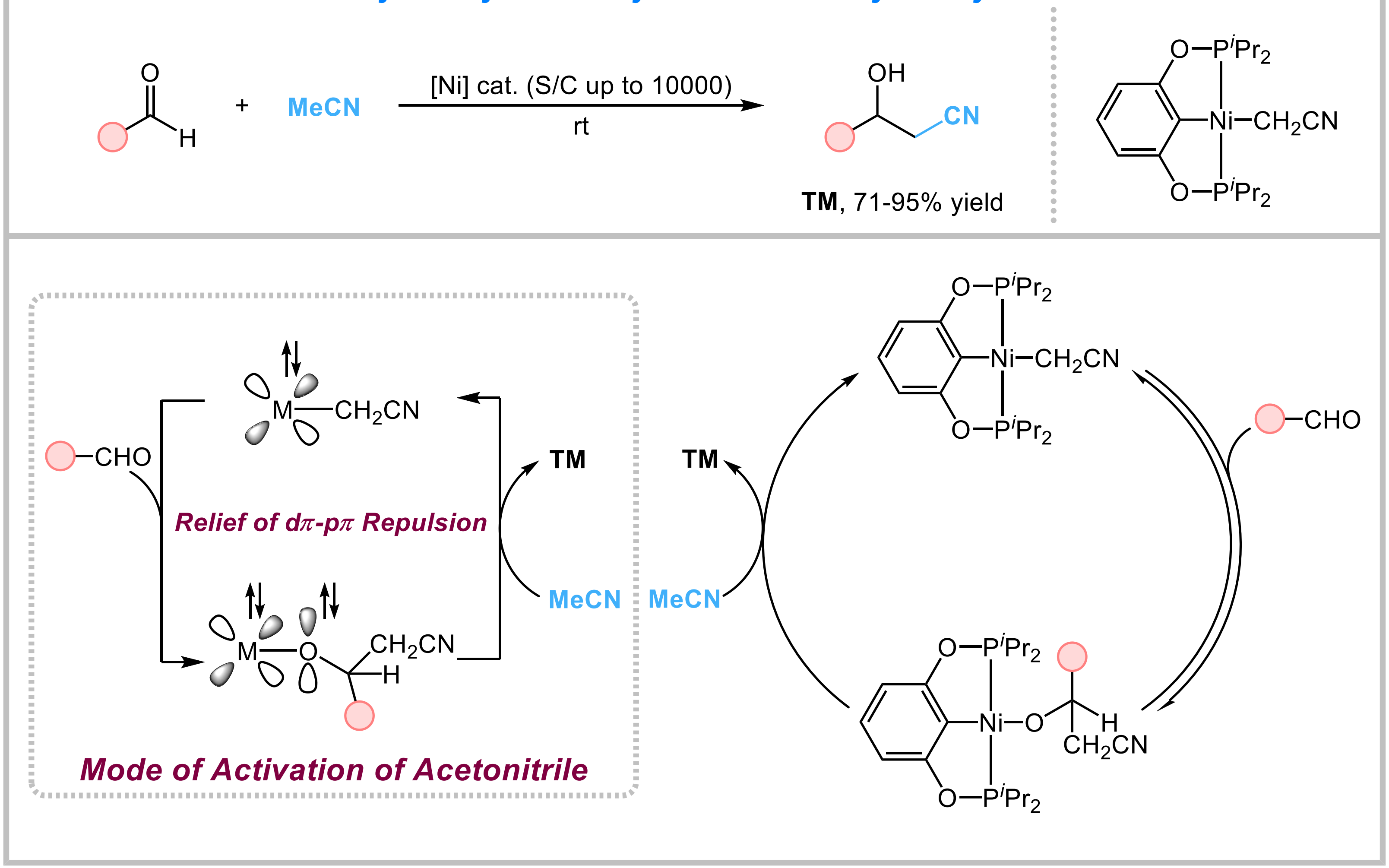
Mn-Catalyzed Michael Addition of Aliphatic Nitriles



Nerush, A.; Vogt, M.; Milstein, D. *J. Am. Chem. Soc.* **2016**, *138*, 6985

Direct Functionalization of Alkyl Nitriles

Nickel-Catalyzed Cyanomethylation of Aldehydes by Acetonitriles



Chakraborty, S.; Patel, Y. J.; Krause, J. A.; Guan, H. *Angew. Chem. Int. Ed.* **2013**, *52*, 7523

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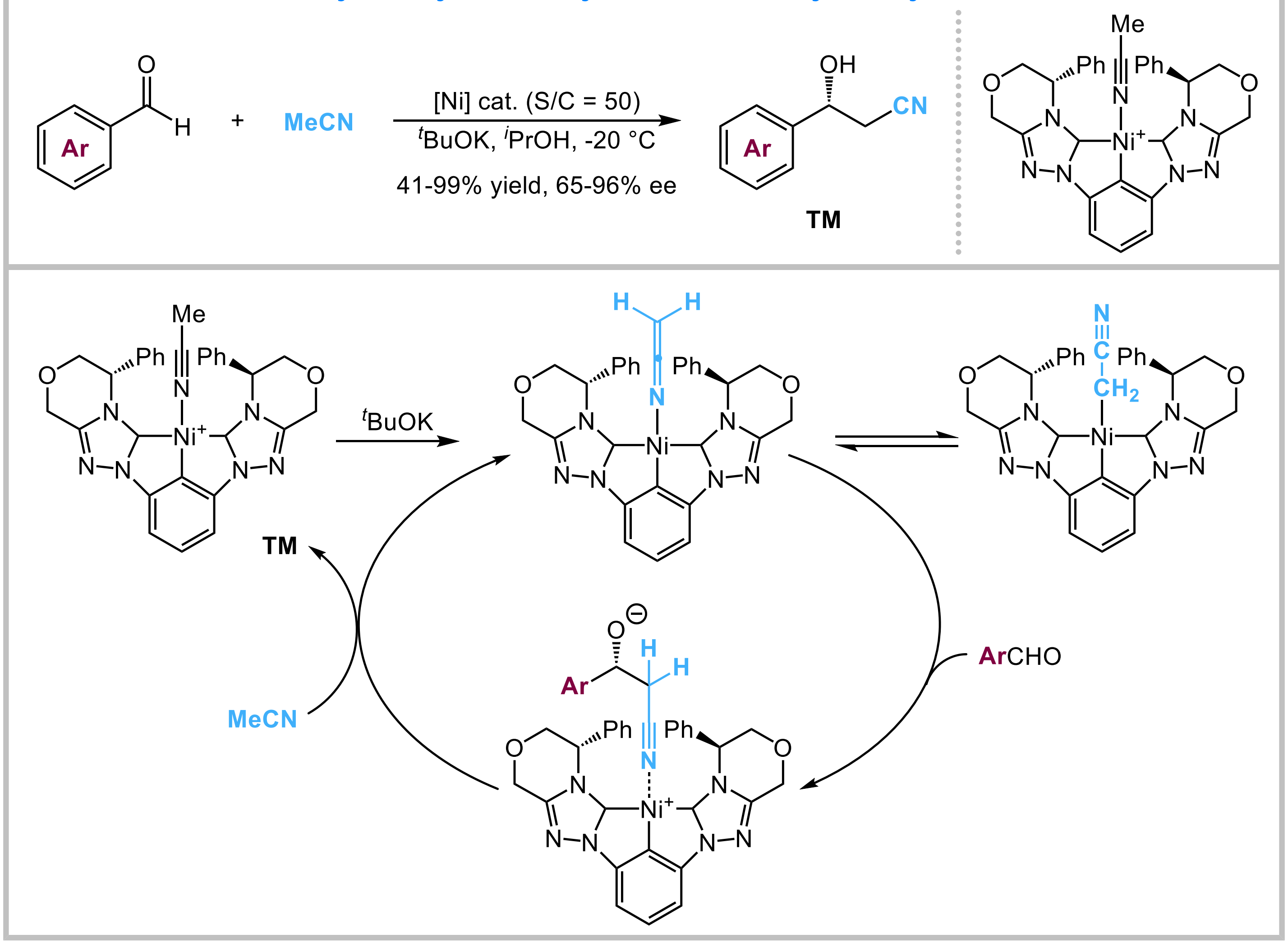
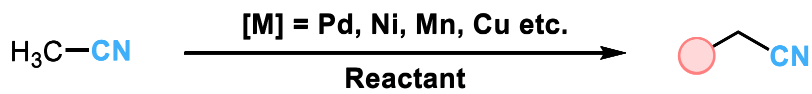
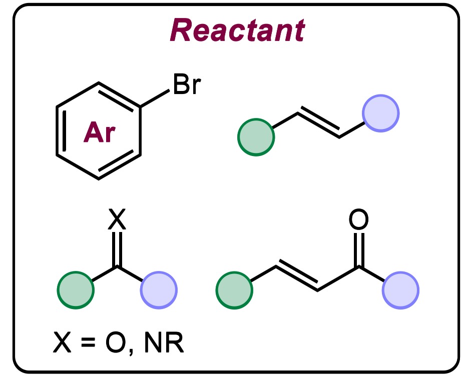


Saito, A.; Adachi, S.; Kumagai, N.; Shibasaki, M. *Angew. Chem. Int. Ed.* **2021**, *60*, 8739

Introduction

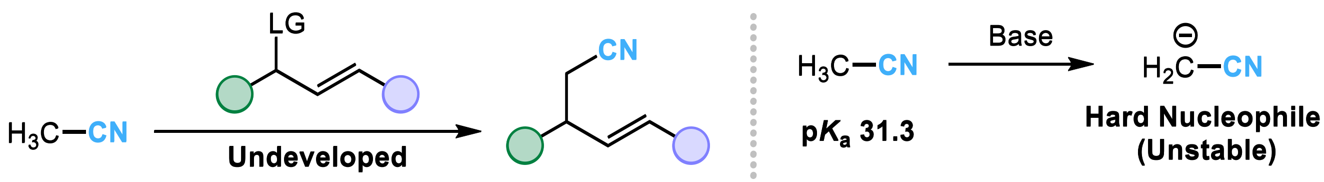
Summary of the Direct Functionalization of Alkyl Nitriles



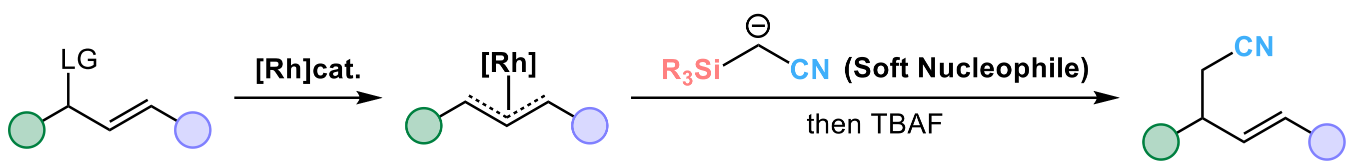


- ♦ Reactant limited
- ♦ Stoichiometric bases normally required
- ♦ Enantioselectivity difficult to control

Catalytic Allylic Cyanomethylation



- ♦ Acetonitrile carbanion difficult to form by mild base
- ♦ Hard to control enantioselectivity in allylic substitution



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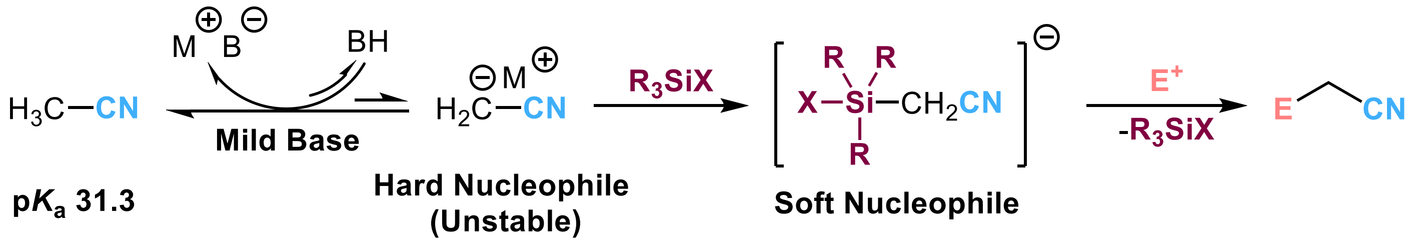
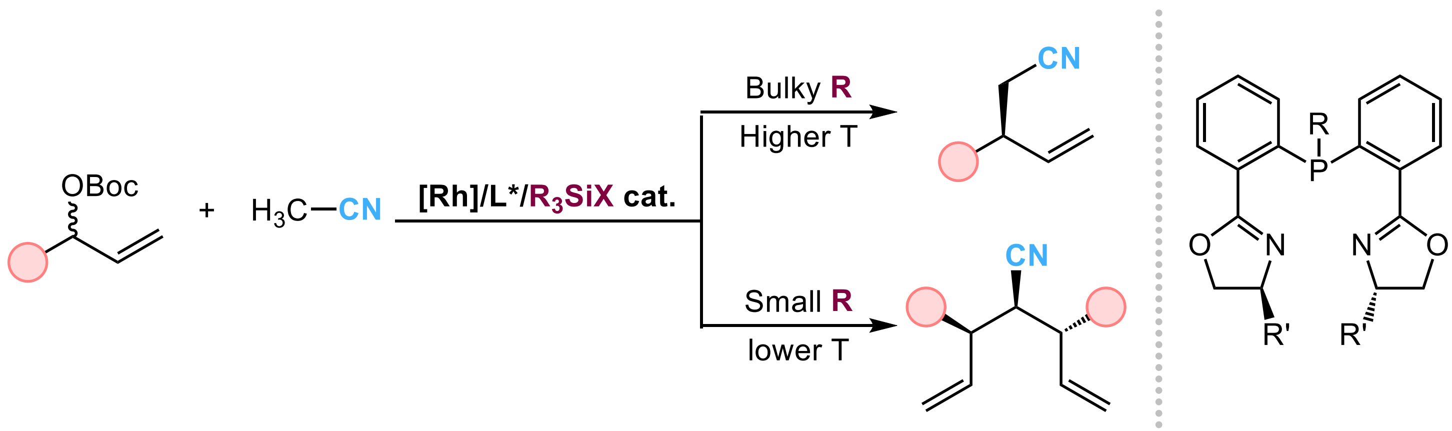
Allylic Cyanomethylation with Acetonitrile

Activation Acetonitrile with Mild Base and Neutral Silicon

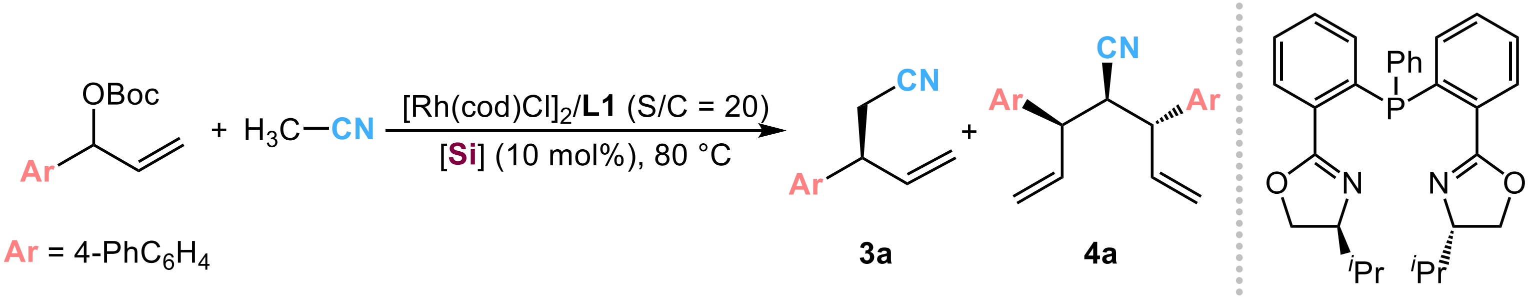


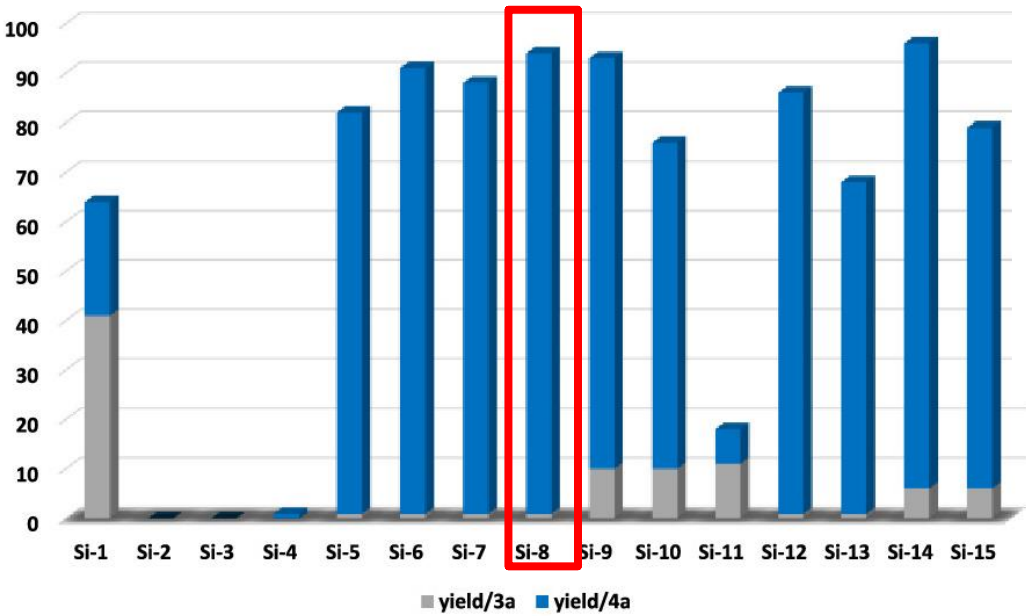
Allylic Cyanomethylation by Rh/Silane Catalysis



Allylic Cyanomethylation with Acetonitrile

Effect of Different Silicon Reagents





Si-1 spirobisilafluorene

Si-2 TMSOTf

Si-3 TMSI

Si-4 Et_4Si

Si-5 $TMSCF_3$

Si-6 $TMSCH_2CO_2Et$

Si-7 $PhMe_2SiCH_2CO_2Et$

Si-8 $TMSCH_2CN$

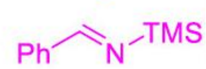
Si-9 $TBSCH_2CN$

Si-10 $TIPSCH_2CN$

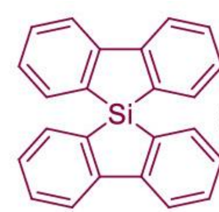
Si-11 TMSO*t*-Bu

Si-12 Et_3SiH

Si-13 Ph_3SiH

Si-14 

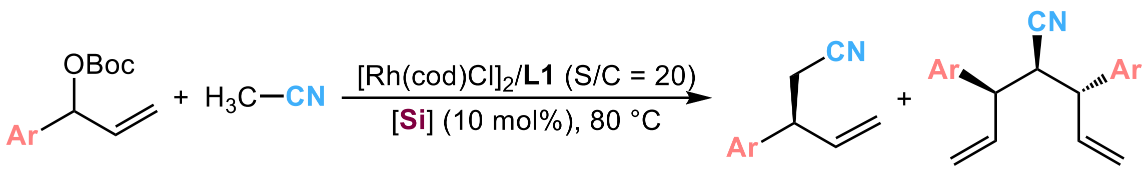
Si-15 $TMSNEt_2$



Si-1

Allylic Cyanomethylation with Acetonitrile

Optimazation of Reaction Conditions



Ar = 4-PhC_6H_4

3a **4a**

Si-8, TMSCH_2CN

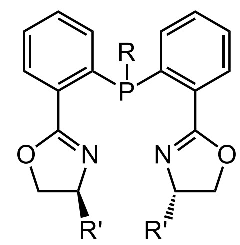
Si-9, TBSCH_2CN

Si-10, TIPSCH_2CN

Entry	[Si]	T (°C)	L	3a, yield (ee) (%)	4a, yield (ee) (%)
1	**Si-8**	80	**L1**	-	93 (99)
2	**Si-8**	80	**L1** (S/C = 50)	-	94 (99)
3	**Si-9**	80	**L1**	9 (99)	88 (99)
4	**Si-10**	80	**L1**	21 (89)	72 (86)
5	**Si-10**	100	**L1**	85 (85)	11 (83)
6	**Si-8**	100	**L1**	6 (99)	88 (98)
7	**Si-10**	100	**L2**	92 (30)	-
8	**Si-10**	100	**L3**	86 (73)	-
9	**Si-10**	100	**L4**	71 (93)	21 (87)
10	**Si-10**	100	**L5**	80 (94)	15 (89)
11	**Si-10**	100	**L6**	93 (97)	-

Reaction Condition: **SM** (0.2 mmol), S/C = 20, and MeCN (1 mL).

Ligand



L1, R = Ph, R' = *i*-Pr

L2, R = Ph, R' = Me

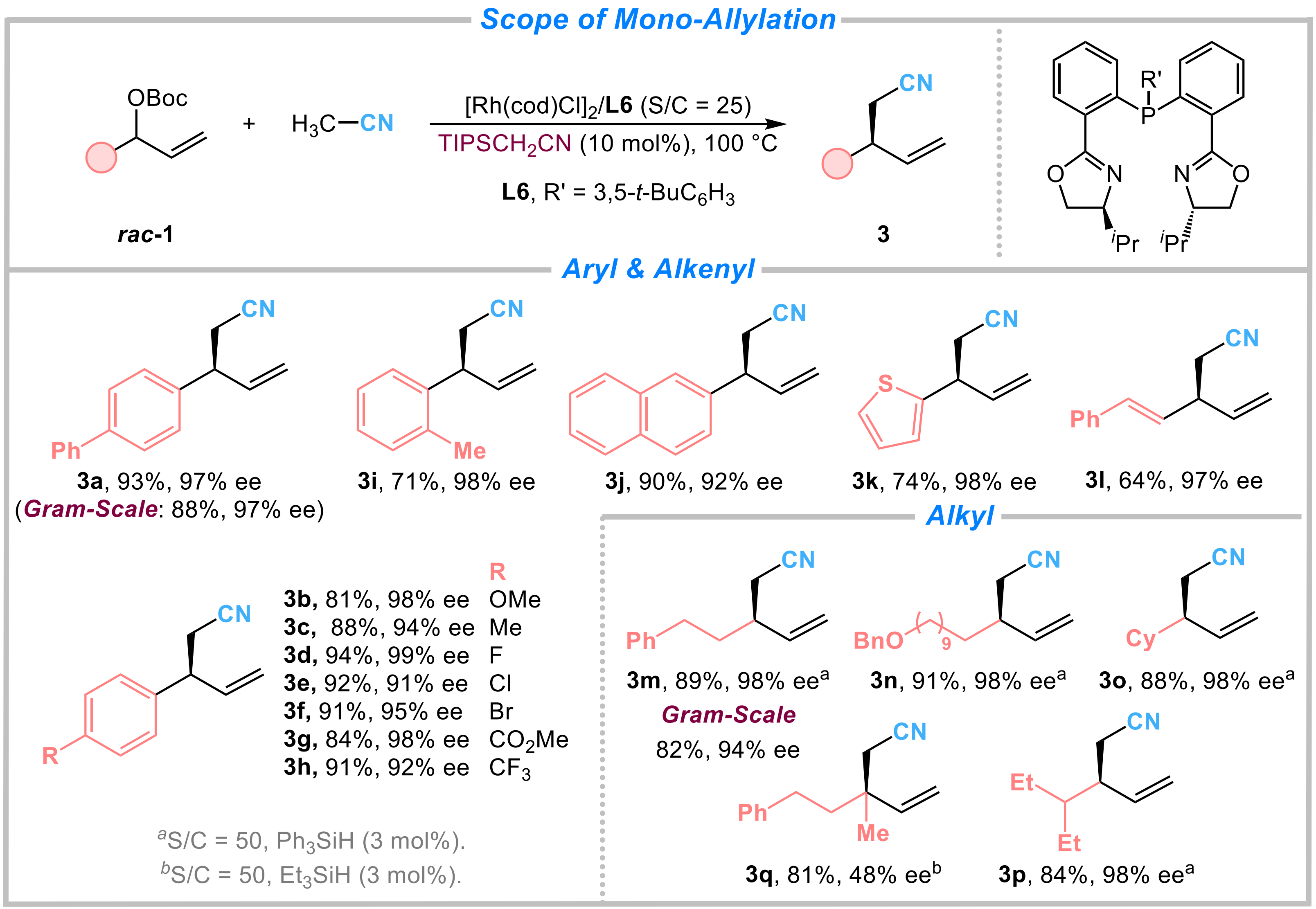
L3, R = Ph, R' = Et

L4, R = Ph, R' = Ph

L5, R = 4-MeO-3,5-*t*-BuC_6H_2, R' = *i*-Pr

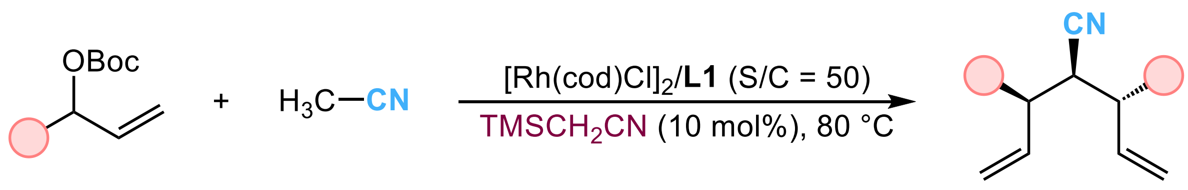
L6, R = 3,5-*t*-BuC_6H_3, R' = *i*-Pr

Allylic Cyanomethylation with Acetonitrile



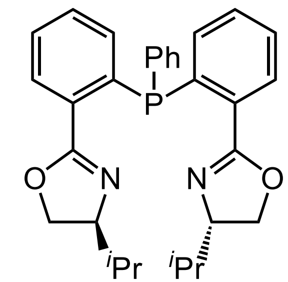
Allylic Cyanomethylation with Acetonitrile

Scope of Bis-Allylation

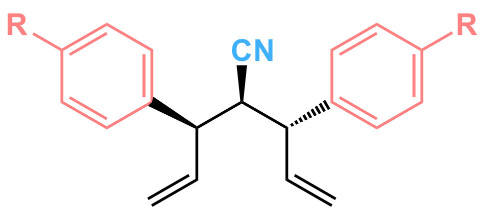


***rac*-1**

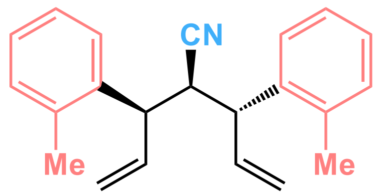
4, dr >20:1



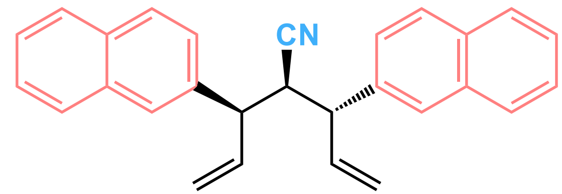
Aryl Group



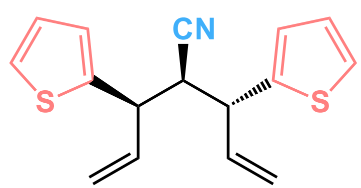
	R
4a, 94%, 99% ee	Ph
4b, 98%, 95% ee	Me
4c, 96%, >99% ee	F
4d, 97%, >99% ee	Cl
4e, 90%, >99% ee	Br
4f, 98%, >99% ee	CF_3
4g, 87%, >99% ee	OMe
4i, 91%, 98% ee	CO_2Me



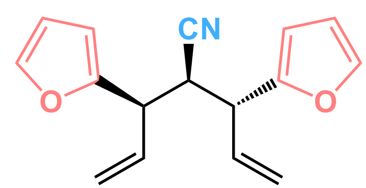
4h, 84%, 98% ee



4j, 96%, 99% ee

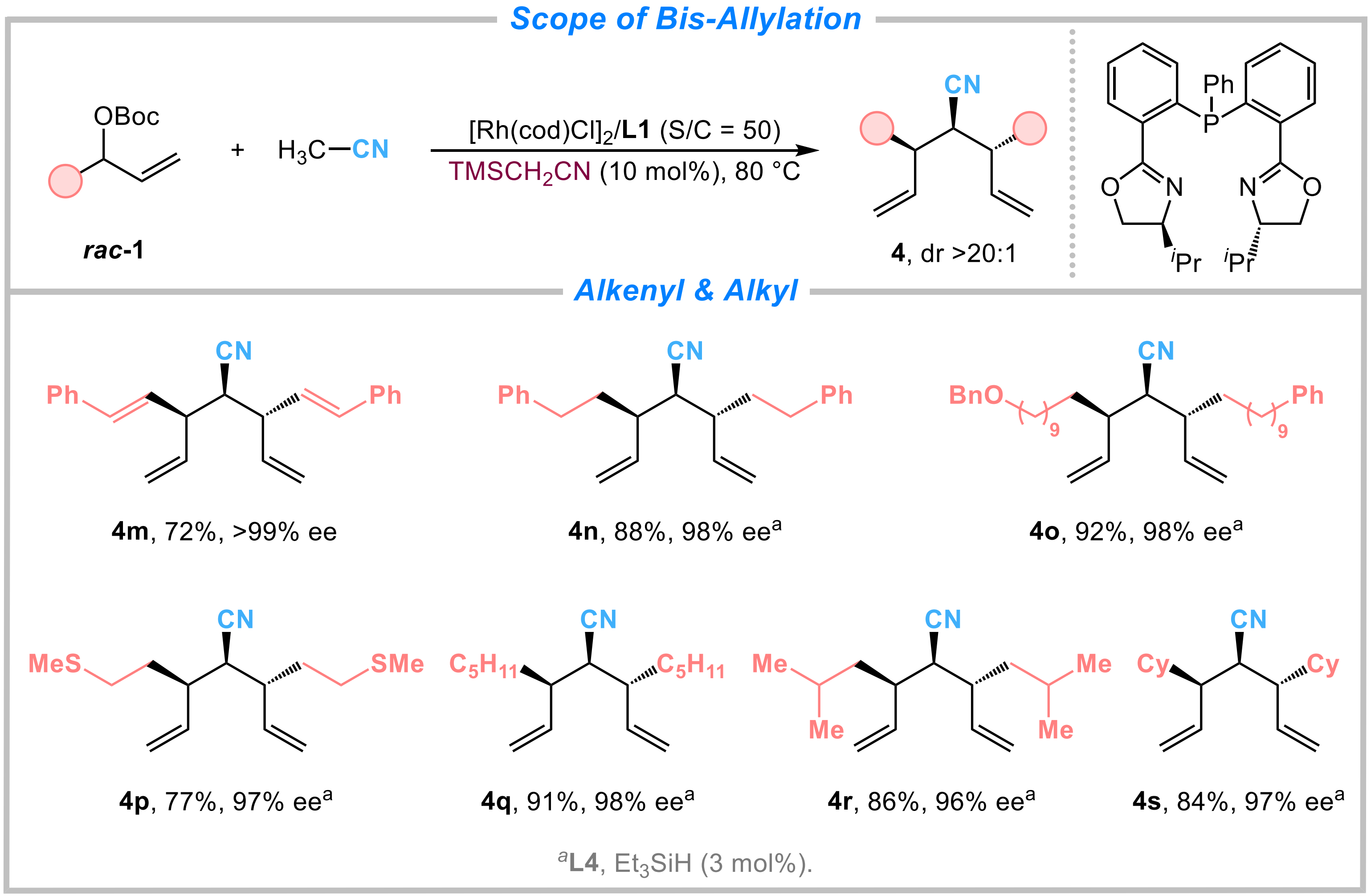


4k, 83%, >99% ee

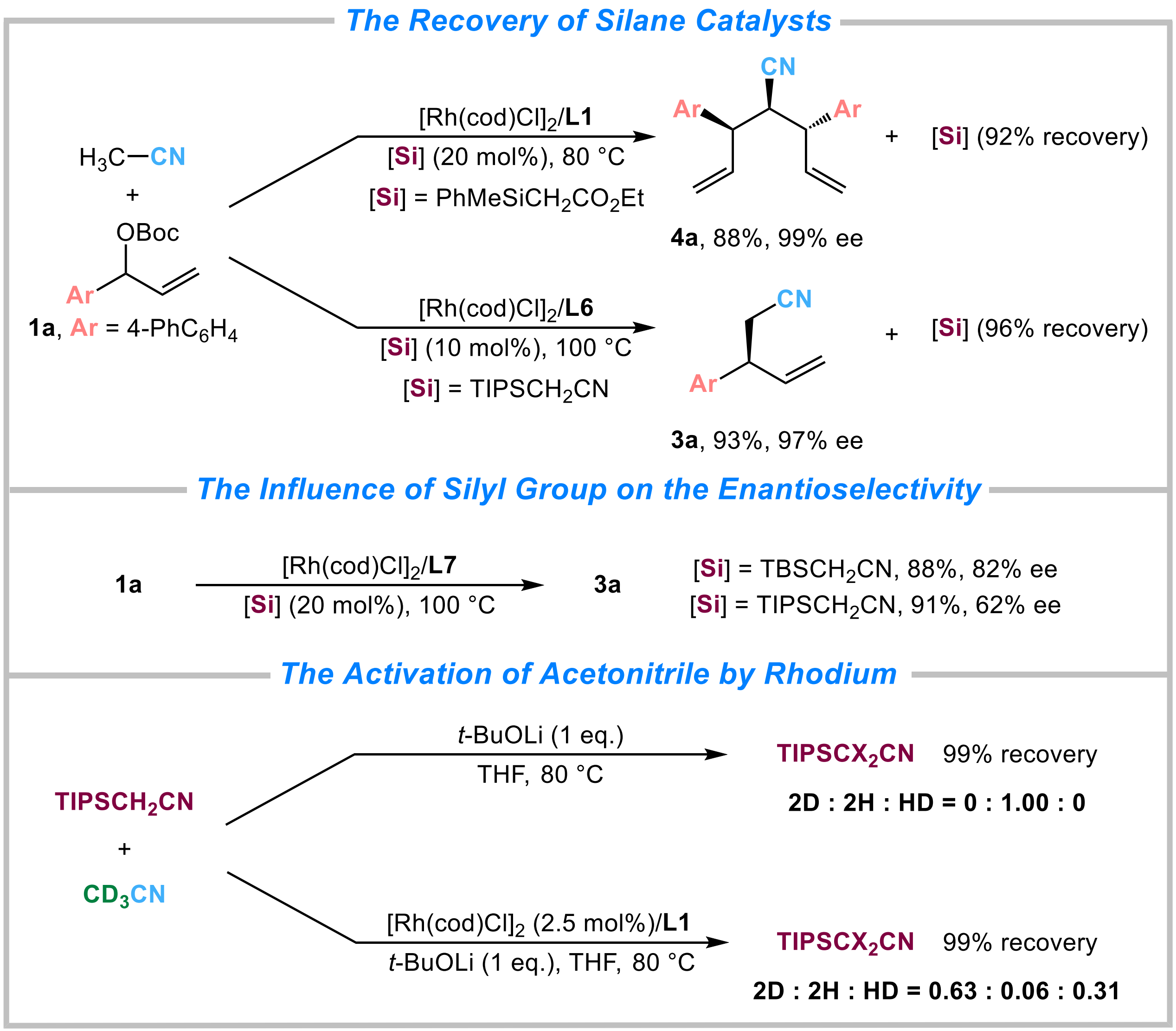


4l, 89%, 98% ee

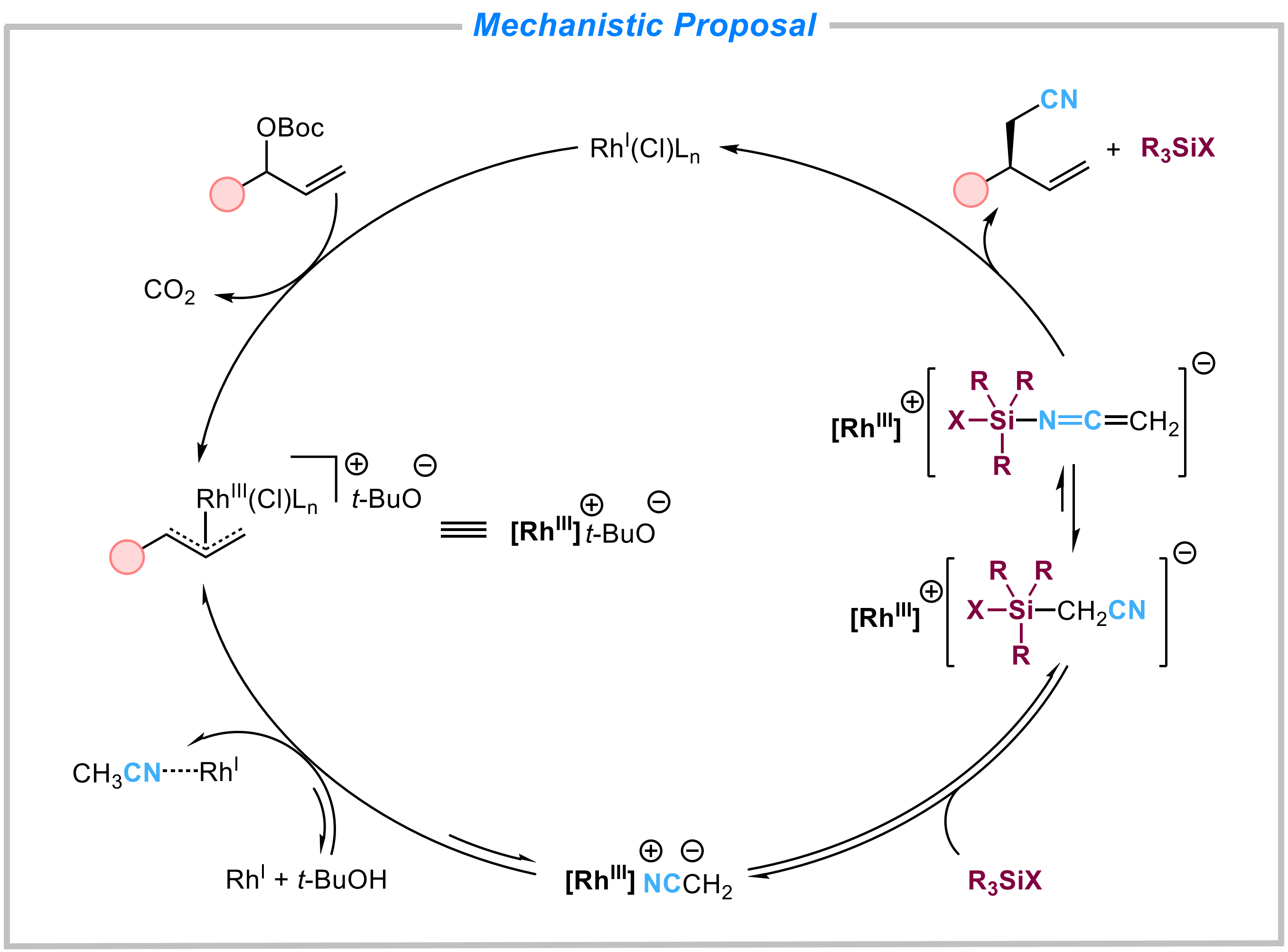
Allylic Cyanomethylation with Acetonitrile



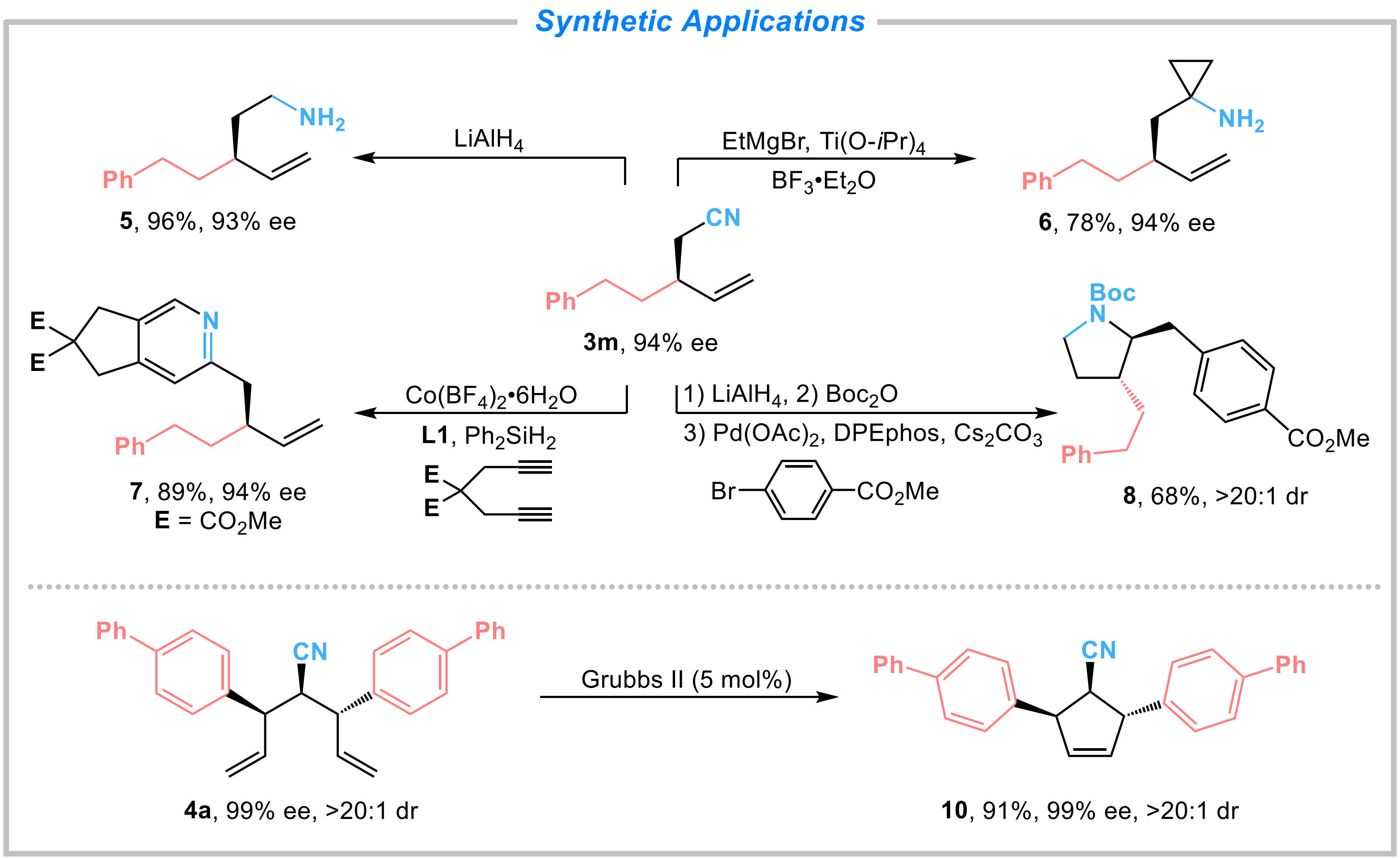
Allylic Cyanomethylation with Acetonitrile



Allylic Cyanomethylation with Acetonitrile

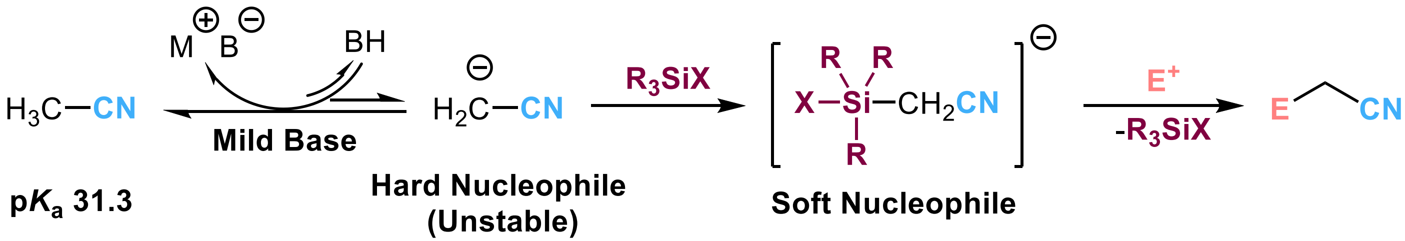


Allylic Cyanomethylation with Acetonitrile

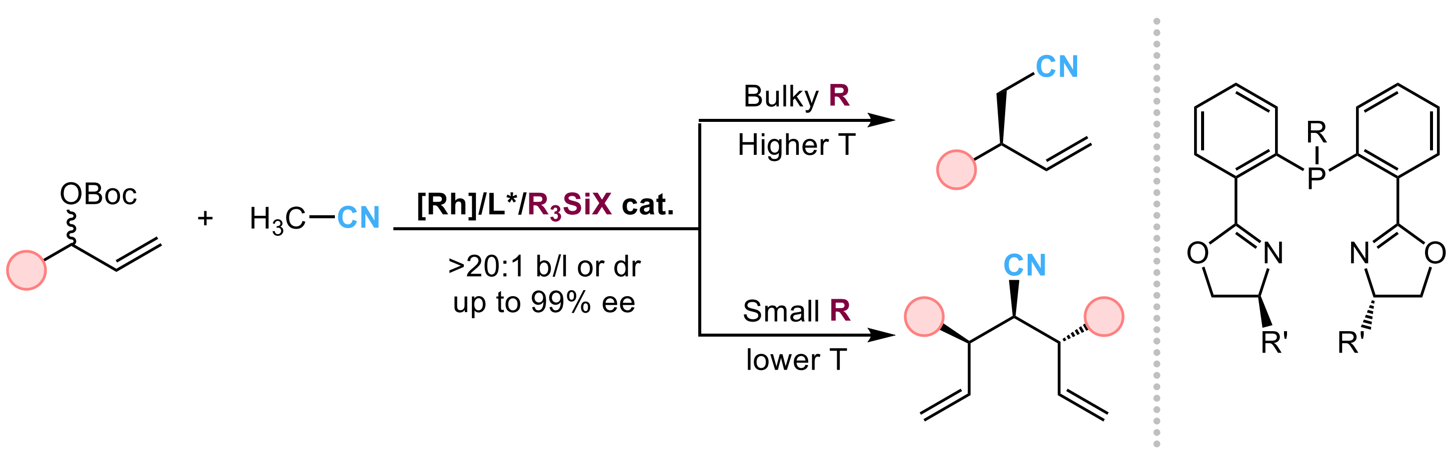


Summary

Activation Acetonitrile with Mild Base and Neutral Silicon



Allylic Cyanomethylation by Rh/Silane Catalysis



♦ ***First Direct Allylic Cyanomethylation of Readily Available Acetonitrile***

♦ ***Rh/Silane-Cocatalyzed Regio- and Enantioselective Allylic Cyanomethylation***

♦ ***Mono- and Bis-Allylation Products Swithable***

Writing Strategies

☐ The First Paragraph

The importance of direct functionalization of alkyl nitriles

↓

Few reports about asymmetric catalysis

↓

The necessity to develop new approach

- ✓ Compared with methods from cyanide and activated nitriles, the direct functionalization of alkyl nitriles (especially aceto-nitrile) provides a less-toxic and more atom-economic strategy to prepare substituted nitriles.

- ✓ However, the direct utilization of acetonitrile in asymmetric catalysis is still very limited. Only the enantioselective addition to aldehydes, ketones, and imines have been reported.

- ✓ The development of new acetonitrile activation and steric control strategy in asymmetric catalysis is of great value. Direct allylic cyanomethylation of readily available acetonitrile is never reported.

Writing Strategies

☐ The Last Paragraph

Summary **of this work**

✓ In summary, we have reported a highly branched and enantio-selective allylic alkylation of acetonitrile directly by synergistic rhodium and silane catalysis.

highlights of the current method

✓ A catalytic amount of moderately polarized silane is the key to realize the high reactivity of acetonitrile. A five-coordinated silicate intermediate was proposed by trapping the acetonitrile anion. The silane catalyst can not only enhance the reactivity, but also switch the mono- and bis-allylation pathways by its size effect.

Outlook **of this work**

✓ The extension of the catalytic silicate formation strategy to other nucleophiles is ongoing in our group.

Representative Examples

- ✓ We envisioned that the addition of R_3SiX may trap and **tame** (*v.* **驯化；驯服；控制**) the acetonitrile anion.

- ✓ Herein, we present a highly branched and enantioselective allylic cyanomethylation from acetonitrile directly by **synergistic** (*adj.* **协同的；协作的**) rhodium and silane catalysis.

- ✓ In light of the relatively poor efficiency, we **elected to explore** (**elect to do sth. 决定做某事**) the impact of base on the reaction.

Acknowledgement

Thanks for your attentions!