JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS
Communication

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

Minghe Sun, Linsheng Wei, and Changkun Li*

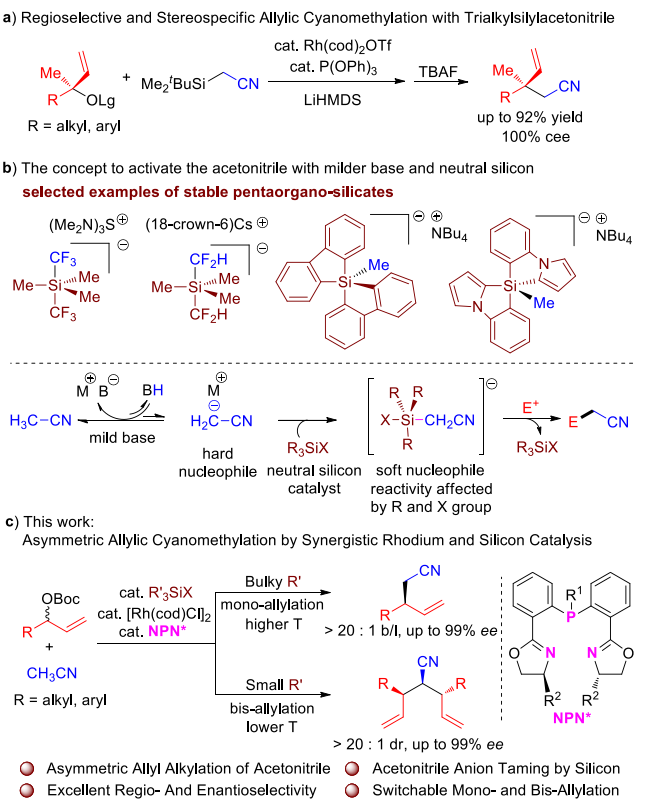
Cite This: J. Am. Chem. Soc. 2023, 145, 3897−3902
Read Online
ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Rh/silane-cocatalyzed regio- and enantioselctive allylic cyanomethylation with inert acetonitrile directly has been developed. Addition of a catalytic amount neutral silane reagent as an acetonitrile anion carrier is essential for the success of this reaction. The synthesis of mono- and bis-allylation products can be switched by adjusting the size of substituents on the silane, ligands, and temperature. Chiral homoallylic nitriles could be synthesized in above 20:1 branch/linear ratio, up to 98% yield and >99% *ee*.

Alkylnitriles widely exist in natural products and biologically active molecules.[1] Nitriles are also frequently utilized as versatile organic intermediates in the synthesis of acids, esters, amides, amines, and other functional groups.[2] Compared with methods from cyanide and activated nitriles,[3] the direct functionalization of alkyl nitriles (especially acetonitrile) provides a less-toxic and more atom-economic strategy to prepare substituted nitriles. Acetonitrile is commonly used as solvent for its inertness and weak acidity (pK_a = 31.3 in DMSO).[4] Stoichiometric strong bases are normally required in the alkylation of acetonitrile, which limits the functional group tolerance and may result in byproducts formation.[5] Several activation modes of acetonitrile based on transition metals[6] and radical process[7] have been developed under milder conditions. 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.[8] The development of new acetonitrile activation and steric control strategy in asymmetric catalysis is of great value.

Transition-metal-catalyzed regio- and enantioselective allylic substitution reactions is one of the most powerful methods to construct carbon−carbon bonds.[9] Although acetonitrile surrogates have been successfully applied in allylation reactions,[10] direct allylic cyanomethylation of readily available acetonitrile is never reported. Reaction of acetonitrile under strong basic conditions led to the Thorpe condensation before allylation.[11] Evans reported an elegant Rh-catalyzed regioselective and stereospecific allylic cyanomethylation with stoichiometric amount of trialkylsilylacetonitrile (Scheme 1a).[10a] Recently, our group developed catalyst based on Co/Rh and bisoxazolinephosphine (NPN*) to realize asymmetric allylic substitution reactions of various acidic pronucleophiles.[12] However, attempts to extend nucleophiles to acetonitrile failed, probably due to the fact that the deprotonation of acetonitrile by the released alkoxide anion is not efficient enough to form a hard and reactive acetonitrile anion. Inspired by Evans' work and the successful isolation of pentaorgano-silicates from reactive carbon anions and neutral

Scheme 1. Asymmetric Allylic Cyanomethylation Enabled by Silicon Reagents



Received: January 8, 2023
Published: February 8, 2023

https://doi.org/10.1021/jacs.3c00244
J. Am. Chem. Soc. 2023, 145, 3897−3902

silicons,[13] we envisioned that the addition of R_3SiX may trap and tame the acetonitrile anion. The good balance between stability and reactivity of silicates enables soft pentaorganosilicate nucleophiles formation from a hard acetonitrile anion (Scheme 1b). Moreover, the substituents on silane can affect the reactivity and selectivity in the allylation. Herein, we present a highly branched and enantioselective allylic cyanomethylation from acetonitrile directly by synergistic rhodium and silane catalysis. The size of R groups in a catalytic amount of silane plays the key role to switch mono- or bis-allylation (Scheme 1c).

We tested the effect of different silicon reagents with racemic allylic carbonate **1a**, acetonitrile **2a**, $[Rh(cod)Cl]_2$, and **L1** at 80 °C (Figure 1). To our delight, the addition of **Si-1** with

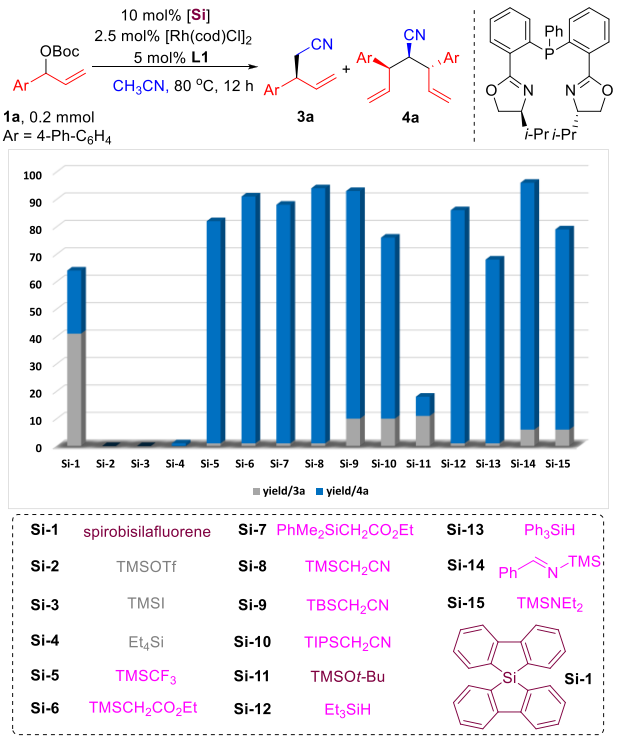


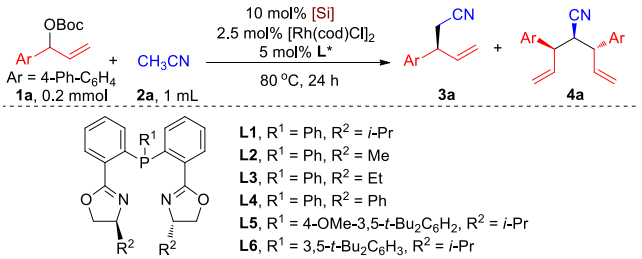
Figure 1. Effect of different silicon reagents.

stabilizing biphenyldiyl groups[13a] leads to the formation of both monoallylation **3a** and bis-allylation **4a** in moderate yields. Further silicon screening indicates that the degree of Si-X polarization should be moderate. **Si-2** and **Si-3** with excellent leaving groups are not reactive, probably due to the direct attack of base to silicon. **Si-4** with nonpolar ethyl groups cannot catalyze the reaction.

Silanes with electron-withdrawing CF_3, CH_2CO_2Et, and CH_2CN groups are all efficient (**Si-5**–**Si-10**) and bis-allylation **4a** is formed predominantly. Low yield was obtained with TMSO*t*-Bu (**Si-11**), which excludes that in situ generated **Si-11** from **Si-8** is the active silicon. Trialkyl or triphenyl silanes **Si-12** and **Si-13** are also reactive. A silyl imine or silylated amine from acetonitrile reduction[14] might be the active catalyst. The silyl imines can be detected by GC-MS after reactions. This was supported by the high reactivity of **Si-14** and **Si-15** with imine or diethylamino groups.

Bis-allylic product **4a** with 99% *ee*[15] and >20:1 dr was obtained in 93% yield after addition of 10 mol % $TMSCH_2CN$ (Table 1, entry 1). The yield and *ee* did not decrease when 1

Table 1. Optimization for Rh-Catalyzed Asymmetric Allylic Cyanomethylation[a]



entry	L	[Si]	**3a**, yield (*ee*), %	**4a**, yield (*ee*), %
1	**L1**	**Si-8**		93 (99)
2[b]	**L1**	**Si-8**		94 (99)
3	**L1**	**Si-9**	9 (99)	88 (99)
4	**L1**	**Si-10**	21 (89)	72 (86)
5[c]	**L1**	**Si-10**	85 (85)	11 (83)
6[c]	**L1**	**Si-8**	6 (99)	88 (98)
7[c,d]	**L2**	**Si-10**	92 (30)	
8[c]	**L3**	**Si-10**	86 (73)	
9[c]	**L4**	**Si-10**	71 (93)	21 (87)
10[c]	**L5**	**Si-10**	80 (94)	15 (89)
11[c]	**L6**	**Si-10**	93 (97)	

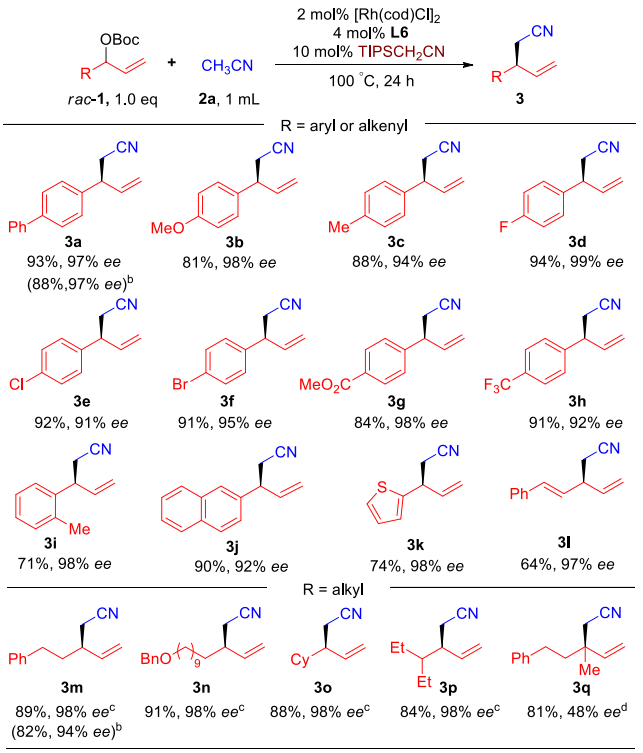
[a]Conditions: **1a** (0.2 mmol, 1.0 equiv), [**Si**] (10 mol%), $[Rh(cod)Cl]_2$ (2.5 mol%), **L** (5 mol%). [b]1 mol% $[Rh(cod)Cl]_2$ and 2 mol% **L1**. [c]100 °C. [d]60 h.

mol % $[Rh(cod)Cl]_2$ is used (entry 2). The bis-allylation could be explained by the β-aryl and olefin enhanced acidity of α-H of nitrile **3a**,[16] which makes the monoallylation challenging. The bigger size of silyl groups in **Si-9** and **Si-10** led to high ratio of **3a** (entries 3 and 4). 85% of **3a** in 85% *ee* was isolated at 100 °C with **Si-10** (entry 5). **Si-8** at 100 °C can only lead to 6% of **3a** (entry 6), which indicates both size of silicon and temperature are important for monoallylation. Higher temperature may accelerate the exchange between **2a** and **3a** in the Rh(I)/nitrile complex (see mechanism scheme). Ligand screening demonstrates that **L6** with bulkier R^1 can further increase the monoselectivity and *ee* (entries 7–11).

The scope of the monoallylation was evaluated (Scheme 2). Both electron-donating and electron-withdrawing groups could be tolerated at the 4-position of the phenyl group in allylic carbonates (**3a**–**3h**). The desired monoallylation products were obtained in high yields and *ee*. The 2-methyl group on phenyl leads to lower conversion (**3i**). 2-Naphthyl, 2-thiophenyl, and styryl substituted allylic carbonates can also be converted to monoallylation products successfully (**3j**–**3l**). Unfortunately, a large amount of 1,3-diene byproduct from β-hydride elimination was obtained when alkyl-substituted allylic substrates were used in the identical condition due to the slower C–C bond formation. Further screening indicates that Ph_3SiH is much more effective even with lower Rh loading. The in situ formed silyl imine[14] is more reactive than $TIPSCH_2CN$, probably due to the more polar Si–N bond. Allylic carbonates bearing phenylethyl and ether groups were tolerated (**3m**, **3n**). **3o** and **3p** with more hindered cyclohexyl and 3-pentyl groups could also be obtained successfully. Finally, **3q** with an all-carbon quaternary carbon center could be prepared in 81% yield, although lower 48% *ee* was obtained. Both **3a** and **3m** can be synthesized in gram scale. When other alkylnitriles were used, the α-allylation product could not be obtained under standard or other conditions, probably due to

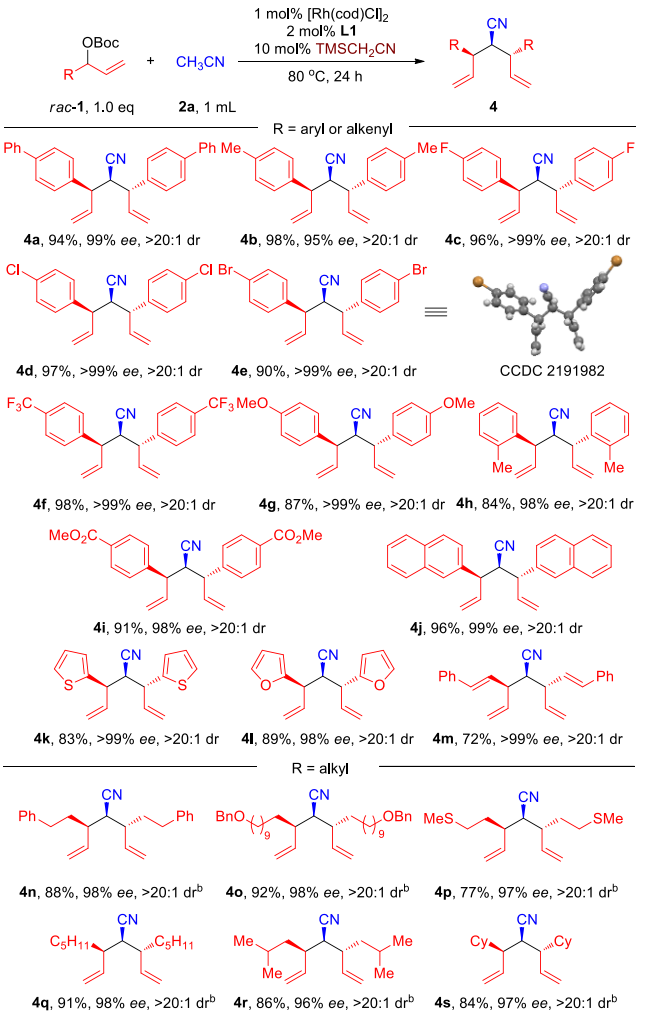
https://doi.org/10.1021/jacs.3c00244
J. Am. Chem. Soc. 2023, 145, 3897–3902

Scheme 2. Scope of Mono-Allylation[a]



[a]Conditions: **1** (0.2 mmol, 1.0 equiv), **Si-10** (10 mol%), $[Rh(cod)Cl]_2$ (2 mol%), **L6** (4 mol%). [b] Gram-scale synthesis. [c] 1 mol% $[Rh(cod)Cl]_2$, 2 mol% **L1** and 3 mol% Ph_3SiH for 10 h. [d] 1 mol% $[Rh(cod)Cl]_2$, 2 mol% **L1** and 3 mol% Et_3SiH for 10 h.

Scheme 3. Scope of Bis-Allylation[a]



[a]Conditions: **1** (0.2 mmol, 1.0 equiv), **2** (1 mL), $TMSCH_2CN$ (**Si-8**, 10 mol%), $[Rh(cod)Cl]_2$ (1 mol%), **L1** (2 mol%). [b] 3 mol% Et_3SiH (**Si-12**) and 2 mol% **L4** were used instead, 10 h.

their lower acidity. The alkylnitrile anion with relatively larger size might be difficult to react with neutral silanes to form pentaorganosilicate and easier to be protonated. The desired product could be obtained indirectly from 2-(trimethylsilyl) alkyl nitriles (see Supporting Information).

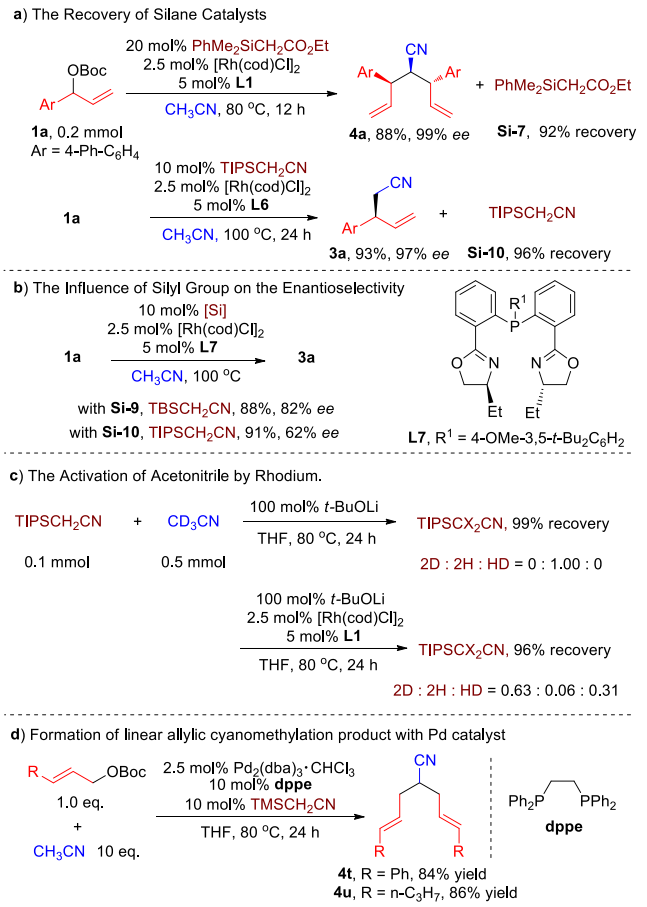
In the bis-allylation reaction (Scheme 3), both electron-donating and electron-withdrawing groups could be tolerated on the phenyl ring to give high yields, above 20:1 diastereomeric ratio and excellent *ee* (**4a**−**4i**). Similarly, heterocyclic and styryl groups make no significant difference on the reactivity and stereoselectivity (**4j**−**4m**). As for alkyl-substituted allylic substrates, 1 mol % $[Rh(cod)Cl]_2$, 2 mol % **L4**, and 3 mol % less hindered Et_3SiH at 80 °C for 10 h was identified as an efficient condition. Bis-allylation products bearing phenylethyl, ether, thioether, and *n*-pentyl groups were obtained in high yields and *ee* (**4n**−**4q**). It is worth mentioning that the more sterically hindered isobutyl and cyclohexyl groups can be introduced to give **4r** and **4s**.

Control experiments were conducted to gain mechanistic insight of the Rh-catalyzed asymmetric allylation of acetonitrile. First, when catalytic amount of $PhMe_2SiCH_2CO_2Et$ (**Si-7**, 20 mol %) and $TIPSCH_2CN$ (**Si-10**, 10 mol %) were subjected to the bis- and monoallylation conditions, respectively, both of the silicon catalysts could be mostly recovered (Scheme 4a). It was demonstrated that the silane catalysts were not converted to other species during the reactions.[17] Second, the substituents on the silyl groups can affect both the chemo- and enantioselectivity of **3a** (Scheme 4b), which indicates a silicon-bonded nucleophile might be really involved. Deuterium exchange between $TIPSCH_2CN$ and CD_3CN was investigated in the presence of LiO^tBu (Scheme 4c). No any deuteration in $TIPSCH_2CN$ was observed after heating in THF at 80 °C for 24 h. However, when Rh(I) and **L1** were added, quite a lot of deuterium was incorporated into the recovered $TIPSCH_2CN$. This result indicates that the deprotonation of acetonitrile was assisted by Rh(I) complex.[18] This result also suggests that the formation of carbon-bounded pentaorgano-silicates might be reversible. Both CH_2CN and CD_2CN moieties in the silicate generated from $TIPSCH_2CN$ can be transferred out. Finally, the promotion effect of silane catalyst is not only limited to rhodium catalysis. The linear selective bisallylation of acetonitrile can be realized with catalytic amounts of Pd(0)/dppe and $TMSCH_2CN$ (Scheme 4d). **4t** and **4u** could be isolated in high yield from linear allylic carbonate **1v** and **1w**, respectively. The monoallylated acetonitrile is easier than simple acetonitrile to undergo the allylation under the catalysis of Pd(0) and silane due to the higher acidity of the α-H of monoallylated acetonitrile.

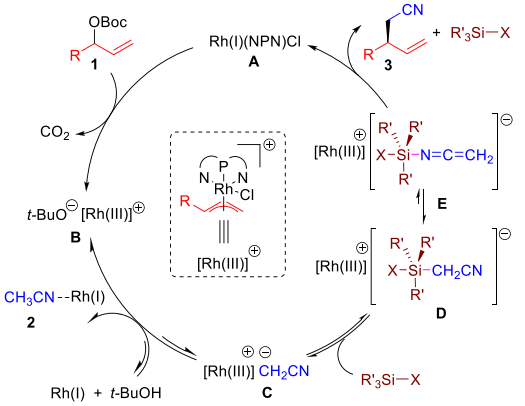
Based on the experiments above and literature reports, a catalytic cycle was proposed in Scheme 5. First, Rh(I)Cl/NPN complex undergoes oxidative addition with allyl *t*-butyl carbonate **1** to form an ionic pair **B** of cationic 18-electron

https://doi.org/10.1021/jacs.3c00244
J. Am. Chem. Soc. 2023, 145, 3897−3902

Scheme 4. Control Experiments



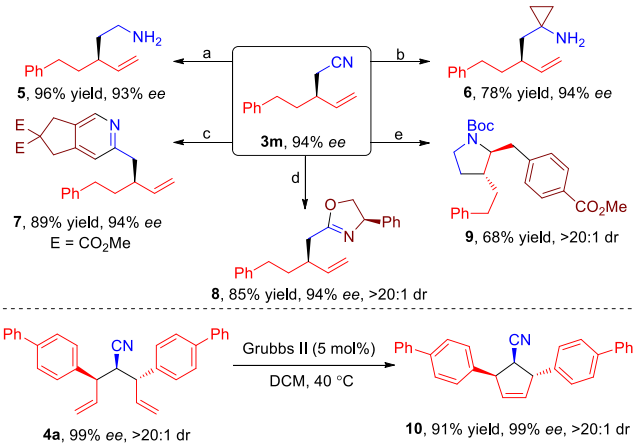
Scheme 5. Mechanistic Proposal



π-allyl/rhodium intermediate and *t*-BuO anion. Deprotonation of Rh(I)-activated acetonitrile **2** by *t*-BuO anion[18] and the formation of intermediate **C** is less favored due to the low acidity of acetonitrile. However, this process can be accelerated by reversible trapping the sterically less hindered acetonitrile anion with neutral silicon reagent, and 5-coordinated silicate based ionic pair **D** was formed.[19] The competing reaction between bulky *t*-butoxide anion and R'_3SiX is reversible and can be suppressed when large R′ group is attached to Si. More active silicate in **E**[20] from the isomerization of **D** attacks the carbon of allyl/Rh intermediate in an outer-sphere manner generates product **3**, releasing Rh(I) **A** and silane reagent. **3** is more acidic than **2** and could undergo another allylation. The bulkier R′ groups in silane R'_3SiX prevents the formation of **D**-type intermediate in the second allylation and stops the reaction at monoallylation **3**.

The chiral homoallylic nitriles could be converted to different chiral products by manipulating the cyano and olefin functions (Scheme 6). The homoallylic nitrile **3m** could be transformed to chiral γ-stereogenic primary amine **5**, cyclopropylamine **6**, pyridine **7**, and oxazoline **8** in single steps, respectively, without any erosion of the enantioselectivity. Chiral pyrrolidine **9** was synthesized in 68% overall yield and >20:1 dr by reduction, protection, and Pd-catalyzed carboamination sequence. Cyano-substituted cyclopentene **10** with 99% *ee* could be synthesized by ring-closing-metathesis of bis-allylated acetonitrile **4a** in 91% yield.

Scheme 6. Synthetic Applications of Homoallylic Nitriles[a]



[a]Conditions: (a) $LiAlH_4$; (b) EtMgBr, $Ti(Oi\text{-}Pr)_4$, $BF_3{\cdot}OEt_2$; (c) dimethyl 2,2-di(prop-2-yn-1-yl)malonate, $Co(BF_4)_2{\cdot}6H_2O$, **L1**, Ph_2SiH_2; (d) (*S*)-2-aminopropan-1-ol, $ZnCl_2$; (e) (1) $LiAlH_4$, (2) $(Boc)_2O$, (3) methyl 4-bromobenzoate, $Pd(OAc)_2$, DPEphos, Cs_2CO_3.

In summary, we have reported a highly branched and enantioselective allylic alkylation of acetonitrile directly by synergistic rhodium and silane catalysis. 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. Chiral nitriles bearing one or two allyl groups were synthesized in above 20:1 branch/linear ratio, up to 98% yield and >99% *ee*. The extension of the catalytic silicate formation strategy to other nucleophiles is ongoing in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c00244.

Detailed experimental procedures, characterization data, copies of ^1H, ^{13}C NMR spectra, HPLC spectra, and X-ray crystal structure of **4e** (PDF)

Accession Codes

CCDC 2191982 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge

https://doi.org/10.1021/jacs.3c00244
J. Am. Chem. Soc. 2023, 145, 3897−3902

via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

Changkun Li − *Shanghai Key Laboratory for Molecular Engineering of Chiral Drugs, School of Chemistry and Chemical Engineering Frontiers Science Center for Transformative Molecules, Shanghai Jiao Tong University, Shanghai 200240, China;* orcid.org/0000-0002-4277-830X; Email: chkli@sjtu.edu.cn

Authors

Minghe Sun − *Shanghai Key Laboratory for Molecular Engineering of Chiral Drugs, School of Chemistry and Chemical Engineering Frontiers Science Center for Transformative Molecules, Shanghai Jiao Tong University, Shanghai 200240, China*

Linsheng Wei − *Shanghai Key Laboratory for Molecular Engineering of Chiral Drugs, School of Chemistry and Chemical Engineering Frontiers Science Center for Transformative Molecules, Shanghai Jiao Tong University, Shanghai 200240, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.3c00244

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work is supported National Natural Science Foundation of China (NSFC) (grant 22171181) and the starting fund of Shanghai Jiao Tong University.

REFERENCES

(1) For selected reviews, see: (a) Fleming, F. F. Nitrile-Containing Natural Products. *Nat. Prod. Rep.* **1999**, *16*, 597−606. (b) Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. Nitrile-Containing Pharmaceuticals: Efficacious Roles of the Nitrile Pharmacophore. *J. Med. Chem.* **2010**, *53*, 7902−7917.

(2) (a) Rappoport, Z. *The Cyano Group*; Wiley: New York, 1970. (b) Fleming, F. F.; Wang, Q. Unsaturated Nitriles: Conjugate Additions of Carbon Nucleophiles to a Recalcitrant Class of Acceptors. *Chem. Rev.* **2003**, *103*, 2035−2078.

(3) For cyanide and activated nitriles, see: (a) Enders, D.; Shilvock, J. P. Some Recent Applications of α-Amino Nitrile Chemistry. *Chem. Soc. Rev.* **2000**, *29*, 359−373. (b) Kurono, N.; Ohkuma, T. Catalytic Asymmetric Cyanation Reactions. *ACS Catal.* **2016**, *6*, 989−1023. (c) Fleming, F. F.; Shook, B. C. Nitrile Anion Cyclizations. *Tetrahedron* **2002**, *58*, 1−23. (d) Palomo, C.; Oiarbide, M.; López, R. Asymmetric Organocatalysis by Chiral Brønsted Bases: Implications and Applications. *Chem. Soc. Rev.* **2009**, *38*, 632−653. (e) Yazaki, R.; Kumagai, N.; Shibasaki, M. Direct Catalytic Asymmetric Addition of Allyl Cyanide to Ketones via Soft Lewis Acid/Hard Brønsted Base/Hard Lewis Base Catalysis. *J. Am. Chem. Soc.* **2010**, *132*, 5522−5531. (f) Denmark, S. E.; Wilson, T. W. Silyl Ketene Imines: Highly Versatile Nucleophiles for Catalytic, Asymmetric Synthesis. *Angew. Chem., Int. Ed.* **2012**, *51*, 9980−9992. (g) Lin, S.; Kawato, Y.; Kumagai, N.; Shibasaki, M. Catalytic Asymmetric Mannich-Type Reaction of N-Alkylidene-α-Aminoacetonitrile with Ketimines. *Angew. Chem., Int. Ed.* **2015**, *54*, 5183−5186. (h) Turnbull, B. W. H.; Evans, P. A. Enantioselective Rhodium-Catalyzed Allylic Substitution with a Nitrile Anion: Construction of Acyclic Quaternary Carbon Stereogenic Centers. *J. Am. Chem. Soc.* **2015**, *137*, 6156−6159. (i) Balaji, P. V.; Brewitz, L.; Kumagai, N.; Shibasaki, M. Achiral Trisubstituted Thioureas as Secondary Ligands to Cu^{I} Catalysts: Direct Catalytic Asymmetric Addition of α-Fluoronitriles to Imines. *Angew. Chem., Int. Ed.* **2019**, *58*, 2644−2648.

(4) Bordwell, F. G. Equilibrium Acidities in Dimethyl Sulfoxide Solution. *Acc. Chem. Res.* **1988**, *21*, 456−463.

(5) For reviews on stoichiometric amounts of strong bases, see: (a) Yang, X.; Fleming, F. F. C- and N-Metalated Nitriles: The Relationship between Structure and Selectivity. *Acc. Chem. Res.* **2017**, *50*, 2556−2568. For other selected examples, see: (b) Culkin, D. A.; Hartwig, J. F. Synthesis, Characterization, and Reactivity of Arylpalladium Cyanoalkyl Complexes: Selection of Catalysts for the α-Arylation of Nitriles. *J. Am. Chem. Soc.* **2002**, *124*, 9330−9331. (c) Yoshizawa, K.; Toyota, S.; Toda, F. Efficient Solvent-Free Thorpe Reactions. *Green Chem.* **2002**, *4*, 68−70. (d) Katritzky, A. R.; Abdel-Fattah, A. A. A.; Wang, M. Expedient Acylations of Primary and Secondary Alkyl Cyanides to α-Substituted β-Ketonitriles. *J. Org. Chem.* **2003**, *68*, 4932−4934. (e) Ji, Y.; Trenkle, W. C.; Vowles, J. V. A High-Yielding Preparation of β-Ketonitriles. *Org. Lett.* **2006**, *8*, 1161−1163. (f) Pitta, B. R.; Steward, O. W.; Fleming, F. F. Electrophile-Dependent Alkylations of Lithiated 4-Alkoxyalk-4-enenitriles. *J. Org. Chem.* **2018**, *83*, 2753−2762.

(6) For selected recent examples with transition metals, see: (a) Chakraborty, S.; Patel, Y. J.; Krause, J. A.; Guan, H. A Robust Nickel Catalyst for Cyanomethylation of Aldehydes: Activation of Acetonitrile under Base-Free Conditions. *Angew. Chem., Int. Ed.* **2013**, *52*, 7523−7526. (b) López, R.; Palomo, C. Cyanoalkylation: Alkylnitriles in Catalytic C-C Bond-Forming Reactions. *Angew. Chem., Int. Ed.* **2015**, *54*, 13170−13184. (c) Liu, Y.; Yang, K.; Ge, H. Palladium-Catalyzed Ligand-Promoted Site-Selective Cyanomethylation of Unactivated $C(sp^3)$-H Bonds with Acetonitrile. *Chem. Sci.* **2016**, *7*, 2804−2808. (d) Nerush, A.; Vogt, M.; Gellrich, U.; Leitus, G.; Ben-David, Y.; Milstein, D. Template Catalysis by Metal-Ligand Cooperation. C-C Bond Formation via Conjugate Addition of Non-activated Nitriles under Mild, Base-free Conditions Catalyzed by a Manganese Pincer Complex. *J. Am. Chem. Soc.* **2016**, *138*, 6985−6997.

(7) (a) Li, J.; Wang, Z.; Wu, N.; Gao, G.; You, J. Radical Cascade Cyanomethylation of Activated Alkenes to Construct Cyano Substituted Oxindoles. *Chem. Commun.* **2014**, *50*, 15049−15051. (b) Bunescu, A.; Wang, Q.; Zhu, J. Copper-Catalyzed Cyanomethylation of Allylic Alcohols with Concomitant 1,2-Aryl Migration: Efficient Synthesis of Functionalized Ketones Containing an α-Quaternary Center. *Angew. Chem., Int. Ed.* **2015**, *54*, 3132−3135. (c) Chatalova-Sazepin, C.; Wang, Q.; Sammis, G. M.; Zhu, J. Copper-Catalyzed Intermolecular Carboetherification of Unactivated Alkenes by Alkyl Nitriles and Alcohols. *Angew. Chem., Int. Ed.* **2015**, *54*, 5443−5446. (d) Wu, X.; Riedel, J.; Dong, V. M. Transforming Olefins into γ, δ-Unsaturated Nitriles through Copper Catalysis. *Angew. Chem., Int. Ed.* **2017**, *56*, 11589−11593. (e) Zhu, N.; Wang, T.; Ge, L.; Li, Y.; Zhang, X.; Bao, H. γ-Amino Butyric Acid (GABA) Synthesis Enabled by Copper-Catalyzed Carboamination of Alkenes. *Org. Lett.* **2017**, *19*, 4718−4721. (f) Xiao, Y.; Liu, Z.-Q. Free Radical Addition of Nitrile, Ketone, and Ester to Alkyne and the Selectivity Discussion. *Org. Lett.* **2019**, *21*, 8810−8813. (g) Yao, H.; Zhong, X.; Wang, B.; Lin, S.; Yan, Z. Cyanomethylation of the Benzene Rings and Pyridine Rings via Direct Oxidative Cross-Dehydrogenative Coupling with Acetonitrile. *Org. Lett.* **2022**, *24*, 2030−2034.

(8) For a review and references cited, see: (a) Kumagai, N.; Shibasaki, M. A Thirst for Enantioselectivity in Catalytic Addition of Alkylnitriles. *Chem. Lett.* **2019**, *48*, 1322−1327. For selected examples, see: (b) Suto, Y.; Kumagai, N.; Matsunaga, S.; Kanai, M.; Shibasaki, M. Direct Catalytic Aldol-Type Reactions Using RCH_2CN. *Org. Lett.* **2003**, *5*, 3147−3150. (c) Suto, Y.; Tsuji, R.; Kanai, M.; Shibasaki, M. Cu(I)-Catalyzed Direct Enantioselective Cross Aldol-Type Reaction of Acetonitrile. *Org. Lett.* **2005**, *7*, 3757−3760. (d) Kawato, Y.; Kumagai, N.; Shibasaki, M. Direct Catalytic Asymmetric Addition of Acetonitrile to *N*-thiophosphinoylimines.

Chem. Commun. **2013**, *49*, 11227−11229. (e) Lin, S.; Kumagai, N.; Shibasaki, M. Enantioselective Synthesis of α,α-Disubstituted α-Amino Acids *via* Direct Catalytic Asymmetric Addition of Acetonitrile to α-Iminoesters. *Org. Biomol. Chem.* **2016**, *14*, 9725−9730. (f) Saito, A.; Kumagai, N.; Shibasaki, M. Direct Catalytic Asymmetric Addition of Acetonitrile to Aldimines. *Org. Lett.* **2019**, *21*, 8187−8190. (g) Saito, A.; Adachi, S.; Kumagai, N.; Shibasaki, M. Direct Catalytic Asymmetric Addition of Alkylnitriles to Aldehydes with Designed Nickel-Carbene Complexes. *Angew. Chem., Int. Ed.* **2021**, *60*, 8739−8743. (h) Adachi, S.; Saito, A.; Shibasaki, M. Diastereoselective Direct Catalytic Asymmetric Mannich-Type Reactions of Alkylnitriles with a Ni(II)-Carbene Complex. *Org. Lett.* **2022**, *24*, 3901−3906.

(9) For selective recent reviews on asymmetric allylation, see: (a) Hartwig, J. F.; Stanley, L. M. Mechanistically Driven Development of Iridium Catalysts for Asymmetric Allylic Substitution. *Acc. Chem. Res.* **2010**, *43*, 1461−1475. (b) Koschker, P.; Breit, B. Branching Out: Rhodium-Catalyzed Allylation with Alkynes and Allenes. *Acc. Chem. Res.* **2016**, *49*, 1524−1536. (c) Qu, J.; Helmchen, G. Applications of Iridium-Catalyzed Asymmetric Allylic Substitution Reactions in Target-Oriented Synthesis. *Acc. Chem. Res.* **2017**, *50*, 2539−2555. (d) Turnbull, B. W. H.; Evans, P. A. Asymmetric Rhodium-Catalyzed Allylic Substitution Reactions: Discovery, Development and Applications to Target-Directed Synthesis. *J. Org. Chem.* **2018**, *83*, 11463−11479. (e) Rössler, S. L.; Petrone, D. A.; Carreira, E. M. Iridium-Catalyzed Asymmetric Synthesis of Functionally Rich Molecules Enabled by (Phosphoramidite, Olefin) Ligands. *Acc. Chem. Res.* **2019**, *52*, 2657−2672. (f) Cheng, Q.; Tu, H.-F.; Zheng, C.; Qu, J.-P.; Helmchen, G.; You, S.-L. Iridium-Catalyzed Asymmetric Allylic Substitution Reactions. *Chem. Rev.* **2019**, *119*, 1855−1969. (g) Süsse, L.; Stoltz, B. M. Enantioselective Formation of Quaternary Centers by Allylic Alkylation with First-Row Transition-Metal Catalysts. *Chem. Rev.* **2021**, *121*, 4084−4099. (h) Stivala, C. E.; Zbieg, J. R.; Liu, P.; Krische, M. J. Chiral Amines via Enantioselective π-Allyliridium-*C*,*O*-Benzoate-Catalyzed Allylic Alkylation: Student Training via Industrial-Academic Collaboration. *Acc. Chem. Res.* **2022**, *55*, 2138−2147.

(10) (a) Tom, M.-J.; Evans, P. A. Regioselective and Stereospecifific Rhodium-Catalyzed Allylic Cyanomethylation with an Acetonitrile Equivalent: Construction of Acyclic β-Quaternary Stereogenic Nitriles. *J. Am. Chem. Soc.* **2020**, *142*, 11957−11961. (b) Han, M.; Yang, M.; Wu, R.; Li, Y.; Jia, T.; Gao, Y.; Ni, H. L.; Hu, P.; Wang, B. Q.; Cao, P. Highly Enantioselective Iridium-Catalyzed Coupling Reaction of Vinyl Azides and Racemic Allylic Carbonates. *J. Am. Chem. Soc.* **2020**, *142*, 13398−13405. (c) Matsunami, A.; Takizawa, K.; Sugano, S.; Yano, Y.; Sato, H.; Takeuchi, R. Synthesis of Chiral Homoallylic Nitriles by Iridium-Catalyzed Allylation of Cyanoacetates. *J. Org. Chem.* **2018**, *83*, 12239−12246. (d) Tom, M.-J.; Evans, P. A. Asymmetric Rhodium-Catalyzed Allylic Substitution Reactions with Nitrile-Stabilized Carbanions. *Synlett.* **2022**, *33*, 939−951.

(11) Bai, D.-C.; Liu, X.-Y.; Li, H.; Ding, C.-H.; Hou, X.-L. Tandem Thorpe Reaction/Palladium Catalyzed Asymmetric Allylic Alkylation: Access to Chiral β-enaminonitriles with Excellent Enantioselectivity. *Chem.—Asian J.* **2017**, *12*, 212−215.

(12) For cobalt/NPN*-catalyzed asymmetric allylic substitution, see: (a) Ghorai, S.; Chirke, S. S.; Xu, W.-B.; Chen, J.-F.; Li, C. Cobalt-Catalyzed Regio- and Enantioselective Allylic Amination. *J. Am. Chem. Soc.* **2019**, *141*, 11430−11434. (b) Ghorai, S.; Rehman, S. U.; Xu, W.-B.; Huang, W.-Y.; Li, C. Cobalt-Catalyzed Regio- and Enantioselective Allylic Alkylation of Malononitriles. *Org. Lett.* **2020**, *22*, 3519−3523. For Rh-catalyzed reactions, see: (c) Xu, W.-B.; Ghorai, S.; Huang, W.; Li, C. Rh(I)/Bisoxazolinephosphine-Catalyzed Regio- and Enantioselective Allylic Substitutions. *ACS Catal.* **2020**, *10*, 4491−4496. (d) Huang, W.-Y.; Lu, C.-H.; Ghorai, S.; Li, B.; Li, C. Regio- and Enantioselective Allylic Alkylation of Terminal Alkynes by Synergistic Rh/Cu Catalysis. *J. Am. Chem. Soc.* **2020**, *142*, 15276−15281. (e) Li, K.; Li, C. Enantioselective Synthesis of 3-Allylindolizines via Sequential Rh-Catalyzed Asymmetric Allylation and Tschitschibabin Reaction. *Org. Lett.* **2020**, *22*, 9456−9461. (f) Sun, M.; Liu, M.; Li, C. Rh-Catalyzed Chemodivergent Regio- and Enantioselective Allylic Alkylation of Indoles. *Chem.—Eur. J.* **2021**, *27*, 3457−3462. (g) Liu, M.; Zhao, H.; Li, C. Rh(I)-catalyzed Regio- and Enantioselective Allylic alkylation of Meldrum's Acid. *Chin. Chem. Lett.* **2021**, *32*, 385−388. (h) Xu, W.-B.; Sun, M.; Shu, M.; Li, C. Rhodium-Catalyzed Regio- and Enantioselective Allylic Amination of Racemic 1,2-Disubstituted Allylic Phosphates. *J. Am. Chem. Soc.* **2021**, *143*, 8255−8260. (i) Li, B.; Liu, M.; Rehman, S. U.; Li, C. Rh-Catalyzed Regio- and Enantioselective Allylic Phosphinylation. *J. Am. Chem. Soc.* **2022**, *144*, 2893−2898.

(13) (a) Deerenberg, S.; Schakel, M.; Keijzer, A. H. J. F. d.; Kranenburg, M.; Lutz, M.; Spek, A. L.; Lammertsma, K. Tetraalkylammonium Pentaorganosilicates: the First Highly Stable Silicates with Five Hydrocarbon Ligands. *Chem. Commun.* **2002**, 348−349. (b) Couzijn, E. P. A.; Schakel, M.; de Kanter, F. J. J.; Ehlers, A. W.; Lutz, M.; Spek, A. L.; Lammertsma, K. Dynamic Configurational Isomerism of a Stable Pentaorganosilicate. *Angew. Chem., Int. Ed.* **2004**, *43*, 3440−3442. (c) Couzijn, E. P. A.; Ehlers, A. W.; Schakel, M.; Lammertsma, K. Electronic Structure and Stability of Pentaorganosilicates. *J. Am. Chem. Soc.* **2006**, *128*, 13634−13639. (d) Prakash, G. K. S.; Wang, F.; Zhang, Z.; Haiges, R.; Rahm, M.; Christe, K. O.; Mathew, T.; Olah, G. A. Long-Lived Trifluoromethanide Anion: A Key Intermediate in Nucleophilic Trifluoromethylations. *Angew. Chem., Int. Ed.* **2014**, *53*, 11575−11578. (e) Chen, D.; Ni, C.; Zhao, Y.; Cai, X.; Li, X.; Xiao, P.; Hu, J. Bis(difluoromethyl)-trimethylsilicate Anion: A Key Intermediate in Nucleophilic Difluoromethylation of Enolizable Ketones with Me_3SiCF_2H. *Angew. Chem., Int. Ed.* **2016**, *55*, 12632−12636.

(14) (a) Gutsulyak, D. V.; Nikonov, G. I. Chemoselective Catalytic Hydrosilylation of Nitriles. *Angew. Chem., Int. Ed.* **2010**, *49*, 7553−7556. (b) Wübbolt, S.; Oestreich, M. Exhaustive Chemoselective Reduction of Nitriles by Catalytic Hydrosilylation Involving Cooperative Si-H Bond Activation. *Synlett* **2017**, *28*, 2411−2414. (c) Takaya, J.; Ogawa, K.; Nakaya, R.; Iwasawa, N. Rhodium-Catalyzed Chemoselective Hydrosilylation of Nitriles to an Imine Oxidation Level Enabled by a Pincer-type Group 13 Metallylene Ligand. *ACS Catal.* **2020**, *10*, 12223−12228.

(15) Harned, A. M. From Determination of Enantiopurity to the Construction of Complex Molecules: The Horeau Principle and Its Application in Synthesis. *Tetrahedron* **2018**, *74*, 3797−3841.

(16) For the NMR analysis of mono- and bis-allylation products, see Supporting Information. Taber, D. F.; Kong, S. *J. Org. Chem.* **1997**, *62*, 8575−8576.

(17) The Si-C bond cleavage in trimethylacetate has been reported, see: Poisson, T.; Gembus, V.; Oudeyer, S.; Marsais, F.; Levacher, V. Product-Catalyzed Addition of Alkyl Nitriles to Unactivated Imines Promoted by Sodium Aryloxide/Ethyl(trimethylsilyl)acetate (ETSA) Combination. *J. Org. Chem.* **2009**, *74*, 3516−3519.

(18) For the activation of acetonitrile by Rhodium, see: (a) Goto, A.; Endo, K.; Ukai, Y.; Irle, S.; Saito, S. Rh^I-Catalyzed Aldol-type Reaction of Organonitriles Under Mild Conditions. *Chem. Commun.* **2008**, 2212−2214. (b) Sureshkumar, D.; Ganesh, V.; Kumagai, N.; Shibasaki, M. Direct Catalytic Addition of Alkylnitriles to Aldehydes by Transition-Metal/NHC Complexes. *Chem.—Eur. J.* **2014**, *20*, 15723−15726.

(19) Another possibility that the acidity enhancement of acetonitrile by activation with neutral silicon catalysis can not be totally excluded currently. Addition of different Lewis acids or transition metals to activate acetonitrile fails to give any desired product (see Supporting Information).

(20) (a) Oertel, A. M.; Ritleng, V.; Chetcuti, M. J.; Veiros, L. F. C-H Activation of Acetonitrile at Nickel: Ligand Flip and Conversion of N-Bound Acetonitrile into a C-Bound Cyanomethyl Ligand. *J. Am. Chem. Soc.* **2010**, *132*, 13588−13589. (b) Qin, W.; Long, S.; Bongini, A.; Panunzio, M. α-Alkyl-α-aryl (Trimethyltin) Nitriles: Versatile Nucleophilic Intermediates in Aldol-Like Reactions. *Eur. J. Org. Chem.* **2015**, *2015*, 3495−3505. (c) Ariafard, A.; Ghari, H.; Khaledi, Y.; Hossein Bagi, A.; Wierenga, T. S.; Gardiner, M. G.; Canty, A. J. Theoretical Investigation into the Mechanism of Cyanomethylation of Aldehydes Catalyzed by a Nickel Pincer Complex in the Absence of Base Additives. *ACS Catal.* **2016**, *6*, 60−68.

https://doi.org/10.1021/jacs.3c00244
J. Am. Chem. Soc. 2023, 145, 3897−3902